DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 352, 700, and 740

[Docket No. 78N–0038]

RIN 0910–AA01

Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) sunscreen drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and new data and information on sunscreen drug products that have come to the agency's attention. FDA is also issuing final rules regarding the labeling of certain cosmetic products to inform consumers that these products do not provide protection from the sun.

EFFECTIVE DATES: This regulation is effective (*insert date 24 months after date of publication in the* **Federal Register**) for parts 310, 352, and 700 and is effective (*insert date 12 months after date of publication in the* **Federal Register**) for part 740.

FOR FURTHER INFORMATION CONTACT: John D. Lipnicki, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

NFR 1

I. Introduction

In the **Federal Register** of August 25, 1978 (43 FR 38206), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking (ANPRM) to establish a monograph for OTC sunscreen drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention Drug Products (the Panel), which was the advisory review panel that evaluated data on the active ingredients in this drug class. The agency's proposed regulation for OTC sunscreen drug products, in the form of a tentative final monograph, was published in the **Federal Register** of May 12, 1993 (58 FR 28194).

In the **Federal Register** of June 8, 1994 (59 FR 29706), the agency proposed to amend the tentative final monograph (and reopened the comment period until August 22, 1994) to remove five sunscreen ingredients because of a lack of interest in establishing United States Pharmacopeia (USP) monographs: Digalloyl trioleate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate, glyceryl aminobenzoate, lawsone with dihydroxyacetone (interest was subsequently shown in developing a monograph for lawsone and dihydroxyacetone), and red petrolatum. The agency also reiterated that all sunscreen ingredients must have a USP monograph before being included in the final monograph for OTC sunscreen drug products. This final rule includes those sunscreen ingredients that have USP monographs.

In the **Federal Register** of September 16, 1996 (61 FR 48645), the agency amended the proposed rule to include avobenzone as a single ingredient and in combination with certain other sunscreen ingredients (interim marketing was allowed in the **Federal Register** of April 30, 1997 (62 FR 23350)). In the **Federal Register** of October 22, 1998 (63 FR 56584), the agency proposed to amend the tentative final monograph to include zinc oxide as a single ingredient and in combination with any proposed Category I sunscreen active ingredient except avobenzone.

In the **Federal Register** of April 5, 1994 (59 FR 16042), the agency reopened the administrative record and announced a public meeting to discuss ultraviolet A (UVA) radiation

claims and testing procedures. In the **Federal Register** of August 15, 1996 (61 FR 42398), the agency reopened the administrative record and announced a public meeting to discuss the photochemistry and photobiology of sunscreens.

This final monograph completes the tentative final monograph except for certain testing issues and UVA labeling, which the agency will discuss in future issues of the **Federal Register**. Until then, UVA labeling may continue in accord with the tentative final monograph and its amendments. The agency advises that on or after (*insert date 24 months after date of publication in the* **Federal Register**), no OTC drug product that is subject to the monograph and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or abbreviated new drug application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

In response to the proposed rule on OTC sunscreen drug products and subsequent reopenings of the administrative record, the agency received 433 comments. The comments included four petitions (Refs. 1 through 4) requesting consideration of sunscreen ingredients that have been marketed in Europe but not in the United States. The status of these petitions is discussed in section II.C, comment 13 of this document. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs if the agency mandated a limit on sun protection factor (SPF) values in this final rule. Copies of the information considered by the Panel, the comments and petitions, and the hearing request are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All ''OTC Volumes'' cited throughout this document refer to information on public display.

A number of comments were filed in the Dockets Management Branch after the dates the administrative record had officially closed. The agency has considered these comments as

''feedback'' communications under the OTC drug review procedures, as discussed in the **Federal Register** of September 29, 1981 (46 FR 47740), and clarified in the **Federal Register** of April 1, 1983 (48 FR 14050). When ''feedback'' material submitted after an administrative record has officially closed directly influences or forms one of the bases for the agency's decision on a matter in an OTC drug rulemaking proceeding, the agency adds it to the administrative record without submission of a formal petition by an interested party.

The agency has included these data and information in the administrative record and addressed them in this document. The agency has considered the request for an oral hearing in its response to the comment and believes it has adequately responded to the manufacturer and that a hearing is not needed. As discussed in section II.G, comment 29 of this document, the agency is allowing the marketing of OTC sunscreen drug products with SPF values above 30 under one collective term (i.e., ''30 plus'' or ''30 +''). The agency will also consider including labeling in the monograph with actual label SPF values on products with SPF values over 30 when adequate data are submitted to substantiate a testing procedure applicable to SPF values over 30.

II. The Agency's Conclusions on the Comments

A. General Comments on OTC Sunscreen Drug Products

1. Several comments asked that the agency either exempt currently marketed sunscreen products from the requirement for redetermining the SPF or provide a 2-year implementation period. One comment requested a 3-year implementation period. The comments contended that the proposed 12-month implementation period would result in lost business and a serious economic hardship for manufacturers, estimated to be 35 million dollars for reformulating, retesting, and relabeling sunscreen products.

The agency agrees with the comments that the proposed 12-month implementation period may cause undue economic burden on some manufacturers of these products without a corresponding benefit to consumers (see section VII of this document). As discussed in section VII, a 24-month

effective date would allow most firms to relabel products during a normal relabeling cycle without incurring additional costs. Accordingly, the final rule will be effective 24 months from the date of this publication. Because this final rule provides testing procedures that were proposed in the tentative final monograph, currently marketed products that have already been tested by those procedures will not need to be retested. However, sunscreen products that have not been tested will need to be tested using the methods described in this document. The agency intends to propose modified test procedures in a future issue of the **Federal Register** and any necessary retesting time will be specified when the final rule for testing procedures publishes.

2. Several comments recommended modifications to the definition of minimal erythema dose (MED) in proposed § 352.3(a). Some comments objected to the presumption that erythema is a ''diffusing'' reaction that starts from within the exposed site and moves outward in a dose dependent manner, i.e., ''redness reaching the borders of the exposure site.'' Other comments asserted that the definition is too limiting because it may not be appropriate for all solar simulator configurations (e.g., no template). Many comments recommended the definition of MED used by the European Trade Association COLIPA (Ref. 5): ''The quantity of radiant energy required to produce the first perceptible, unambiguous redness reaction with clearly defined borders.'' Another comment recommended ''erythema-effective ultraviolet radiation'' in place of ''radiant energy.''

The agency agrees that the proposed definition of MED should be modified for the reasons discussed by the comments and is revising § 352.3(a) in this final rule, as follows: ''*Minimal erythema dose (MED).* The quantity of erythema-effective energy (expressed in Joules per square meter) required to produce the first perceptible redness reaction with clearly defined borders.'' The agency considers this definition broad enough to encompass tests conducted with solar simulator configurations with no template and consistent with COLIPA's definition.

3. One comment noted that the wavelength ranges for UVA, UVB, and UVC radiation in the tentative final monograph differed from the official ranges of the Commission International de L'Eclairage (CIE), which are: (1) UVC–radiation of less than 280 nanometers (nm), (2) UVB–

280 to 315 nm, and (3) UVA–315 to 400 nm. The comment mentioned the agreement reached at the 11th International Congress on Photobiology (Ref. 6) on the short wavelength end of UVB radiation (280 or 290 nm) and suggested that the scientific evidence supports 320 nm as the long-wavelength boundary of UVB radiation.

The agency agrees with the comment that the scientific evidence supports 320 nm as the long-wavelength boundary of UVB radiation. However, the short-wavelength boundary for UVB radiation has been accepted as either 280 or 290 nm. Given that the comment did not provide a compelling reason to change the proposed definition of UVB radiation, the agency will continue to define the boundaries of UVB radiation as 290 to 320 nm.

4. Comments requested the agency to amend the definition of a sunscreen active ingredient in proposed § 352.3(c) to include mechanisms other than absorption, to expand the UV range to include UVA radiation, and to provide a minimum SPF value requirement. The comments added that some proposed Category I active ingredients (e.g., menthyl anthranilate and titanium dioxide) do not meet the proposed definition, and that the definition is not interpretable without specifications for measuring 85 percent absorbance.

The agency discussed the need to modify the definition in a 1996 proposed amendment of the tentative final monograph (61 FR 48645 at 48646). The agency agrees that modifications should be to: (1) Include mechanisms other than absorption, (2) redefine wavelengths, and (3) remove the percent absorbance requirement. The agency does not agree that a minimum SPF value should be included in the definition because this information is more appropriately a characteristic of the final formulation. Therefore, the agency has revised proposed § 352.3(c) in this document, to read: "*Sunscreen active ingredient.* An ingredient listed in § 352.10 that absorbs, reflects, or scatters radiation in the ultraviolet range at wavelengths of 290 to 400 nanometers."

5. One comment recommended that the agency reevaluate statements in the tentative final monograph on the harmful nature of tanning. The agency discussed the harmful effects of UV radiation-induced tanning in the tentative final monograph (58 FR 28194 at 28238 to 28239). The

comment suggested that a natural tan reduces cumulative sun exposure and may potentiate sunscreen effectiveness. The comment did not, however, provide data or references to support this claim or to otherwise cause the agency to change its position.

6. One comment requested that the final monograph require expiration dating and storage information in the labeling of OTC sunscreen drug products. The comment noted that under 21 CFR 211.137, OTC drug products with data demonstrating stability for 3 years and without labeled dosage limitations are not required to include an expiration date in their labeling. The comment stated that it was aware of numerous cases that suggest these products may not be stable for 3 years.

The agency requested the comment to provide data and information about the specific products it was aware of (Ref. 7), but none were subsequently provided. The agency is not currently aware of stability problems that would require expiration dating for OTC sunscreen drug products but will address such a requirement if data become available. All sunscreen active ingredients included in the final monograph also have a USP monograph that contains packaging and storage requirements and standards for products containing these ingredients.

7. Comments recommended that the agency establish procedures for ensuring batch-to-batch SPF test results, and that it approve testing laboratories and regulate their performance.

Regulations already exist to assure that each batch of drug product meets established specifications for the identity and strength of each active ingredient. Specifically, 21 CFR 211.160 requires that product specifications and laboratory controls be established and performed. Although the agency would not require SPF testing on human subjects for every batch produced, manufacturers need to assure conformance to their finished product specifications. Further, any changes to the batch formula would, at a minimum, require review and documentation by the manufacturer's quality control unit to determine if SPF retesting is necessary. Finally, 21 CFR 211.180 provides for the inspection of records pertaining to production, control, and distribution of batches of drug products. Thus, testing laboratories are subject to these regulations.

B. Comments on the Drug/Cosmetic Status of Sunscreen Products

8. One comment questioned whether sunscreen products should be regulated as drugs. The comment asserted that such products are not active in the mitigation or elimination of a disease condition, and that sunscreen products have no more affect on the structure and function of the body than ''being in physical shade.''

The basis for the agency's determination that products intended for use as sunscreens are subject to regulation as drugs under section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(g)(1)) is set forth at length in the tentative final monograph (58 FR 28194 at 28203 to 28206). Essentially, sunscreen active ingredients affect the structure and function of the body by absorbing, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. Proper use of sunscreen ingredients (see section II.L, comment 51 of this document) may help to prevent skin damage and may help reduce the risk of skin lesions, skin cancer, and other disease conditions. Products that are marketed to achieve these important health benefits meet the definition of a drug under section 201(g)(1)(B) and (g)(1)(C) of the act.

9. One comment disagreed with the agency's tentative conclusion that products containing a sunscreen ingredient, but labeled for the purpose of obtaining an ''even tan,'' are subject to regulation as drugs. According to the comment, such a product is subject to regulation as a drug only if it bears a claim to treat or prevent sunburn. The comment asserts that this has been the agency's consistent approach since 1940.

Another comment stated that sunless tanning products, used to impart color without exposure to the sun, could be improved by adding a sunscreen to provide users protection during their normal outside activities. The comment requested that such products should be regarded as cosmetics, because they would be used primarily for a cosmetic effect, with the sunscreen protection serving only a secondary purpose.

The agency thoroughly discussed the regulatory status of ''tanning'' products, including the basis for withdrawing its 1940 advisory opinion on sunburn and suntan preparations, in the tentative final monograph (58 FR 28194 at 28203 to 28207, 28293 to 28294). As discussed in the tentative final monograph, the presence of a sunscreen active ingredient, in conjunction with labeling claims that the product may be used, e.g., to permit tanning or to acquire an even tan, generally establishes that the product's intended use is that of a drug. Such products suggest, among other things, that the ingredients in the product will allow the consumer to stay in the sun longer without suffering skin damage (58 FR at 28204). Likewise, products that claim to accelerate or stimulate the tanning process are claiming, either expressly or impliedly, to stimulate the production of melanin in the body. Such a claim to affect the structure or function of the body renders the product subject to regulation as a drug under section 201(g)(1) of the act (see 58 FR 28194 at 28293). Finally, a sunless tanning product that contains a sunscreen ingredient, to provide protection to the consumer, is subject to regulation as a drug. The idea that the sunburn protection offered by the product may only be a ''secondary'' feature for the consumer is not relevant. If an intended use of the product is to provide users with sun protection when they go outside (as the comment suggests), then the product is subject to regulation as a drug.

On the other hand, products that do not make express or implied sun protection claims, and do not contain sunscreen ingredients, may be regarded as cosmetics under section 201(i) of the act. If the product is intended solely to provide cosmetic effects on the skin (e.g., to moisturize the skin while sunbathing), or solely to impart color to the skin without exposure to the sun or other sources of light (i.e., sunless tanning), then the product may be marketed as a cosmetic. Such products, however, must include a warning statement (discussed in this section, comment 10 of this document) to inform the consumer that the product does not provide any protection against sunburn. Products marketed to enhance or permit tanning that do not contain a sunscreen ingredient must be reviewed on a case-by-case basis to determine whether the product is intended

solely to provide a cosmetic benefit (such as moisturizing) or whether the product is intended to enhance or permit tanning by some other mechanism of action.

The comments offered no other reasoning and no data to the contrary, other than to suggest that the agency's approach would encourage manufacturers to remove sunscreen ingredients from suntan products and, thereby, expose consumers to even higher levels of harmful ultraviolet rays. The agency is not persuaded that a significant number of manufacturers will choose to reformulate their products, to make them less safe for consumers, as a result of this final rule. Moreover, consumers will continue to have an array of sunscreen-containing products from which to choose. Finally, as discussed below, certain tanning products (including sunless tanning products) that do not contain sunscreen ingredients must bear a prominent warning to the consumer. This will ensure that the consumer is fully informed as to which products offer sun protection and which do not.

10. One comment requested that the signal word ''Caution'' replace the signal word ''Warning'' preceding the following statement for suntanning preparations: ''Warning—This product does not contain a sunscreen and does not protect against sunburn.'' The comment stated that the word ''Warning'' suggests safety hazards associated with these products that are unrelated to sunburn. Another comment petitioned to add a second sentence to the warning: ''Tanning in sunlight or under tanning lamps can cause skin cancer and premature skin aging-even if you don't burn.'' The comment concluded that the availability of tanning products without a protective sunscreen ingredient is a serious health issue and detrimental to public health. A third comment objected to any such warnings on tanning products.

The agency considers it an important public health issue that users of suntanning products be alerted when these products do not contain a sunscreen and do not protect against sunburn or other harmful effects to the skin. Because suntanning products are intended for repeated use under the sun or suntanning lamps while acquiring a tan, the agency considers failure to provide information on hazards associated with repeated, unprotected exposure to UV radiation to be a failure to reveal material facts (see sections 201(n), 502(a), and 602(a) of the act (21 U.S.C. 352(a)

and 362(a))), especially in light of the representations that are made for the product (e.g., suntanning). Therefore, the agency is requiring the labeling of suntanning preparations that do not contain a sunscreen ingredient (§ 740.19 (21 CFR 740.19)) to bear the following: ''Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn.'' The agency considers this information to be sufficiently important, for safety reasons, to require a 12-month effective date (as opposed to 24 months for the balance of the rule) and to require the strongest possible signal word, i.e., ''Warning.''

11. One comment disagreed with the proposal that hair care and nail products that contain a sunscreen ingredient for a nontherapeutic use (e.g., to protect the color of the product), and that use the term ''sunscreen'' in the labeling, must describe in the labeling the functional role of the sunscreen. According to the comment, it is highly unlikely that consumers would think that these products are intended to protect the skin. If this requirement were finalized, the comment requested that the agency permit the term ''sunscreen'' to appear once anywhere in the labeling, with the purpose of the sunscreen explained elsewhere in the labeling.

The agency disagrees with the premise of this comment. The use of the term ''sunscreen'' in labeling suggests that the product in some way will protect the consumer from the harmful effects of the sun. The health risks associated with relying on a product for protection from the sun, when in fact the product does not provide such protection, are sufficiently serious to require the type of disclosure outlined in the proposed rule. Information about the purpose of a sunscreen ingredient in a hair care or nail product will be useful to consumers to inform them that the ingredient protects only the hair or only the color of the product.

This information need appear only once and can appear anywhere in the labeling, provided the qualifying purpose appears prominently and conspicuously and in conjunction with the word ''sunscreen.'' The information may, e.g., be combined in a single statement, e.g., ''Contains a

sunscreen—to protect product color." This will ensure that consumers will see and readily associate the two pieces of information.

12. Two comments objected to the use of an OTC drug rulemaking process to change cosmetic labeling requirements, i.e., the addition of a warning on certain tanning products and the labeling requirements for hair care or nail products that contain a sunscreen for a nontherapeutic use.

The agency addressed this procedural concern, which was also raised in response to the ANPRM, at length in the tentative final monograph (58 FR 28194 at 28201 to 28202). The industry and consumers have had ample notice of the fact that this proceeding included several cosmetic labeling issues that arise out of the same facts and findings at issue in developing the OTC drug monograph. It is not uncommon for the agency to address in an OTC rulemaking document the status of, or the regulation of, products that fall outside of the monograph. In this instance, the cosmetic labeling issues were so closely related to the OTC drug issues that a separate proceeding would have been overly duplicative and inefficient.

C. Comments on Specific Sunscreen Active Ingredients

13. Several comments noted that FDA had deferred a decision on the citizen petitions requesting that sunscreen active ingredients marketed solely in foreign countries be included in the OTC sunscreen monograph. The comments urged FDA answer these petitions and establish a policy concerning the inclusion of OTC sunscreens based solely on foreign data and marketing experience.

In the **Federal Register** of October 3, 1996 (61 FR 51625), the agency published an ANPRM that addressed establishing eligibility criteria for considering additional OTC conditions (i.e., OTC drug active ingredients, indications, dosage forms, dosage strengths, routes of administration, and active ingredient combinations) in the OTC drug monograph system. These proposed criteria would address how foreign or domestic OTC marketing experience could be used to support the inclusion of an ingredient in an OTC drug monograph. Specifically, the criteria would address how OTC marketing experience in the United States or abroad could be used to meet the statutory requirement

under section 201(p) of the act of marketing ''to a material extent'' and ''for a material time.'' ''Material extent'' and ''material time'' are needed to qualify a specific OTC drug condition for consideration under the OTC drug monograph system.

The decision on whether to proceed with a final rulemaking on this subject will be based, in part, on the information and comments submitted in response to the notice of proposed rulemaking that the agency is preparing for publication in a future issue of the **Federal Register**. Resolution of the pending sunscreen petitions must await the outcome of any final rulemaking on this subject.

14. One comment requested that the agency adopt simpler, more user-friendly, names for several sunscreen ingredients: (1) Roxadimate for ethyl-[bis(hydroxypropyl)] aminobenzoate, (2) lisadimate for glyceryl aminobenzoate, and (3) diolamine methoxycinnamate for diethanolamine methoxycinnamate. The comment claimed that these names had been adopted or designated by the United States Adopted Names (USAN) Council. The comment also requested that if USAN adopts a name for phenylbenzimidazole sulfonic acid, FDA adopt this name as well. The comment also suggested the use of the acronyms ''TEA'' and ''DEA'' for triethanolamine and diethanolamine, respectively.

The agency is including in this final monograph only those active ingredients that are the subject of an official USP compendial monograph that sets forth its standards of identity, strength, quality, and purity (see section I of this document). In the **Federal Register** of June 8, 1994, FDA deleted ethyl-[bis(hydroxypropyl)] aminobenzoate and glyceryl aminobenzoate from the tentative final monograph due to the lack of interest in establishing USP monographs for these ingredients. Moreover, two sunscreen ingredients (including diethanolamine methoxycinnamate) have been deferred from the final monograph due to the lack of a current or proposed compendial monograph. Therefore, the issue of whether a ''user-friendly'' name for these ingredients should be developed or adopted need not be resolved in this proceeding at this time. Similarly, TEA and DEA need not be addressed in this proceeding, as triethanolamine is not a sunscreen active

ingredient, and diethanolamine is only used in the ingredient diethanolamine methoxycinnamate which, as discussed, is not a monograph ingredient at this time.

With respect to the comment on the monograph ingredient phenylbenzimidazole sulfonic acid, the agency agrees that if USAN or the USP were to adopt a different or alternative name for this ingredient, such a name could be used in the labeling of a product that contains this ingredient. As discussed in comment 30 of the tentative final monograph (58 FR 28194 at 28207 to 28209), the agency is using the compendial name as the established name for each active ingredient.

15. Two comments requested that the term ''PABA'' continue to be allowed in labeling. The comments stated that the name aminobenzoic acid is meaningless to consumers and physicians, who over the years have learned to recognize this ingredient on the label as PABA. One comment recommended the use of aminobenzoic acid in the ingredient list and the use of PABA in other communications about the product. The comment added that the term ''PABA-free'' should be allowed on products that do not contain aminobenzoic acid. The other comment proposed either to permit the listing of the ingredient as PABA or, if that is unacceptable, as PABA (aminobenzoic acid).

In comment 30 of the tentative final monograph (58 FR 28194 at 28207 to 28209), the agency discussed the issue of the appropriate established name for this and other sunscreen ingredients. As the agency stated in that discussion, the recognized compendial name for aminobenzoic acid no longer includes the term PABA.

The agency acknowledges, however, that the term PABA formerly was part of the established name for this ingredient and that the use of the term in consumer labeling has continued despite the change in the compendial name. In addition, the agency agrees with the comment that many consumers have learned to recognize this ingredient as, and only as, PABA. The agency also recognizes that consumers seeking to avoid the use of this ingredient for health-related reasons (e.g., allergy) may, in this case, be misled if the term PABA were no longer permitted. Some consumers may believe that a product that lists aminobenzoic acid as an ingredient, but does not

list PABA, is PABA-free. If such a consumer has an allergy to aminobenzoic acid, the individual may suffer adverse health consequences.

For these reasons, and especially in light of the potential safety concerns for certain consumers, the agency concludes that wherever the ingredient aminobenzoic acid appears in the labeling of an OTC sunscreen drug product, including labeling that notes the absence of this ingredient, the descriptive term PABA must immediately follow the established name, i.e., ''Aminobenzoic acid (PABA).'' Thus, e.g., a product that is currently marketed as ''PABA-free'' would now be required to state that the product is ''Aminobenzoic acid (PABA)-free.'' This convention will allow consumers to begin to recognize that the ingredient they may wish to avoid is ''aminobenzoic acid.'' After a sufficient period of time, the agency will revisit the need for consumer labeling to continue to bear the descriptive term PABA.

16. One comment stated that claims of protection by artificial melanin, melanin-containing products, and antioxidants should be enumerated, well regulated, and defined.

The agency agrees with the comment, but these claims are not covered by this final monograph. Melanin and artificial melanins are not recognized sunscreen active ingredients. Any product containing melanin or artificial melanins as active ingredients and making sun protection claims would have to seek marketing approval under a new drug application (NDA).

The agency is aware that claims of protection from antioxidants are used in the labeling of some cosmetic products with or without a sunscreen. The agency will ascertain the nature of any such claims (drug or cosmetic) on a case-by-case basis.

17. Several comments objected to the agency's proposal that OTC sunscreen drug products must contain less than 500 parts per billion (ppb) of N-methyl-N-nitrosoaminobenzoate octyl ester (NMPABAO) for several reasons: (1) Toxicological studies indicate that NMPABAO does not have mutagenic or suspected carcinogenic potential (Ref. 8), (2) NMPABAO may be present in sunscreens containing padimate O only in small amounts (ppb range) and the risks associated with NMPABAO are very low, (3) NMPABAO decomposes quickly when exposed to UV radiation,

and (4) industry is aware not to formulate with known nitrosating agents in the presence of amines in order to avoid nitrosamine contamination of its products. Some comments stated that FDA's own conclusions in the tentative final monograph concerning the safety of both NMPABAO and padimate O do not support the imposition of concentration limits for NMPABAO in sunscreens nor do they justify the high cost of analyzing each batch of sunscreen product for NMPABAO. One comment contended that any proposed limit should apply to all nitrosamines and not just NMPABAO. The comment stated that nitrosamines can be formed from any secondary or tertiary amine. Several sunscreen active ingredients contain this moiety in their chemical structure and many inactive ingredients are secondary or tertiary amines. The comment concluded that targeting NMPABAO falsely conveys that padimate O is a unique concern, resulting in manufacturers using other ingredients to avoid costly testing and negative implications.

In the tentative final monograph, the agency did not propose a concentration limit on NMPABAO. Rather, based on concerns that had been raised, the agency asked for comment on whether it should consider proposing a fixed limit. As discussed in the tentative final monograph (58 FR 28194 at 28288 to 28293), toxicological studies support the agency's belief that the risk associated with NMPABAO contamination of sunscreen drug products is very low due to NMPABAO's low mutagenicity and carcinogenicity potential and rapid decomposition in the presence of UV radiation. The agency has not become aware of any new data or information since the publication of the tentative final monograph suggesting a safety concern with NMPABAO in sunscreen drug products. Therefore, the agency has decided not to propose or otherwise include in this final monograph a requirement that OTC sunscreen drug products must contain less than 500 ppb of NMPABAO.

In the tentative final monograph (58 FR 28194 at 28292), the agency discussed its analysis for NMPABAO in 25 commercially available sunscreen products. Of the 11 samples found to be contaminated with NMPABAO, the four highest contained 2-bromo-2-nitro-1,3-propanediol, an indirect nitrosating agent. The agency concluded that there would be no nitrosamine contamination

if these products were formulated without the nitrosating agent. As noted by several of the comments, the industry is aware not to formulate with known nitrosating agents in the presence of amines in order to avoid nitrosamine contamination of its products.

18. One comment submitted a reference to a subchronic oral toxicity study in rats conducted with padimate O which a chemical manufacturer had submitted to the Toxic Substance Control Act 8(e) coordinator of the United States Environmental Protection Agency for consideration. The study was a 4-week repeated dose study at doses of 0, 100, 300, and 1,000 milligrams (mg)/ kilogram (kg)/day of padimate O administered by gavage in a corn oil vehicle (10 to 15 rats/ group/sex). The study included a 4-week recovery period to assess the persistence or reversibility of any toxic effects. At the end of the 4-week treatment period, toxic effects were seen in four target organs: Testes, epididymis, spleen, and liver. The no-observed-effect-level in this study was 100 mg/kg/day for both males and females. Toxic effects appeared reversible in the animals necropsied after the 4-week recovery period with the exception of marked epididymal hypospermia at the 1,000 mg/kg/day dose (5/5 animals).

The clinical relevance of this animal toxicity study is difficult to assess. Padimate O was administered chronically and at very high oral doses. Under normal use conditions, sunscreen drug products containing padimate O are applied topically and used intermittently. In addition, pharmacokinetic parameters were not calculated and the different routes of administration (oral in this study versus topical for sunscreen products) preclude calculation of a ''safety margin'' on the basis of dose per unit of body weight or surface area. Similarly, kinetic data are not available for a comparison of serum levels of drug or metabolites. Literature searches indicate no published information on the kinetics of padimate O with topical application in man. If percutaneous absorption of padimate O does occur in man, it seems likely that the peak and/or cumulative levels achieved with sunscreen usage would be quite low compared to the systemic exposure achieved in this animal toxicity study. Further, it is not known whether the irreversible epididymal hypospermia found in the 1,000 mg/kg/day group would also be reversible with more time.

The agency has determined that this study does not present sufficient data to exclude padimate O from the final monograph and that an adequate safety margin exists for its use as an OTC sunscreen ingredient.

19. Two comments submitted safety and/or efficacy data to support Category I status for micronized titanium dioxide (Refs. 9 and 10). One comment stated that micronized titanium dioxide is not a new material but is a selected distribution of existing material that provides higher SPF values while being transparent and esthetically pleasing on the skin. The comments added that micronized titanium dioxide meets all safety and efficacy criteria and also meets the USP specifications for purity except pure water content.

Another comment asserted for the following reasons that micronized titanium dioxide is a new ingredient with several unresolved safety and efficacy issues: (1) It does not meet the definition of a sunscreen opaque sunblock, (2) there is no control of particles to agglomerate, which is critical to effectiveness, (3) no standards exist to ensure integrity of coatings, (4) there are no performance-based standards of identity; micronized titanium dioxide is not included in the USP, (5) its photocatalyst potential, and (6) the potential for the smaller particle size to accumulate under the skin.

The agency finds the data with the comments supportive of monograph status for micronized titanium dioxide. Acute animal toxicity, irritation, sensitization, photoirritation, photosensitization, and human repeat insult patch and skin penetration studies revealed no deleterious effects. SPF values for four product formulations containing from 4.4 to 10 percent micronized titanium dioxide were from 9 to 24 and support effectiveness as a sunscreen ingredient.

The agency is aware that sunscreen manufacturers are using micronized titanium dioxide to create high SPF products that are transparent and esthetically pleasing on the skin. The agency does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of the titanium dioxide originally reviewed by the Panel. Fairhurst and Mitchnick (Ref. 11) note that ''fines'' have been part of commercially used titanium dioxide powders for decades,

and that a micronized product simply refers to a refinement of particle size distribution. Based on data and information presented at the September 19 and 20, 1996, public meeting on the photobiology and photochemistry of sunscreens (Ref. 12), the agency is not aware of any evidence at this time that demonstrates a safety concern from the use of micronized titanium dioxide in sunscreen products. While micronized titanium dioxide does not meet the proposed definition of a sunscreen opaque sunblock, the agency has not included the use of this term in the final monograph (see section II.L, comment 52 of this document). The potential for titanium dioxide particles to agglomerate in formulation, which could result in lower SPF values, is addressed by the final product SPF test. The SPF data that the agency reviewed (Ref. 9) did not indicate such a problem.

Micronized titanium dioxide meets current USP monograph specifications for titanium dioxide with the exception that the material contains more associated water. In both the July through August 1996 and 1998 issues of the *Pharmacopeial Forum* (Refs. 13 and 14), the United States Pharmacopeial Convention published in-process revision proposals to make the monograph for titanium dioxide more applicable to ingredients used in sunscreen drug products. The agency will work with the USP in the future to update this monograph as necessary.

20. One comment stated that it is unnecessary to set the maximum limit of titanium dioxide at 25 percent.

The Panel discussed the safety and effectiveness of 2 to 25 percent titanium dioxide in the ANPRM (43 FR 38206 at 38250) and the agency concurred with the Panel's findings in the tentative final monograph (58 FR 28194 at 28295). The comment submitted no data and the agency has no data to support the use of titanium dioxide in sunscreen drug products at concentrations higher than 25 percent.

D. Comments on Dosages for Sunscreen Drug Products

21. Several comments objected to the minimum concentration requirements for sunscreen active ingredients when used in combination because they: (1) Are a less effective measurement

of effectiveness than a performance based SPF test, (2) impact on creativity and innovation of new formulations (technological advances since publication of the 1978 ANPRM have resulted in higher SPF values using lower concentrations of active ingredients), (3) increase potential for irritation and allergic reactions due to unnecessarily high concentration levels of active ingredients, (4) contradict FDA's position that the lowest effective dose of an active ingredient be used to produce the desired treatment effect, (5) result in higher manufacturing and consumer costs due to unnecessary levels of active ingredients, and (6) affect international harmonization because Canada, Australia, and the European Union have no concentration minimums for active ingredients when used in combination.

One comment petitioned the agency to amend proposed § 352.20 of the tentative final monograph to include a provision for formulating combination sunscreen products at lower minimum concentrations. Two comments submitted efficacy data to support lower concentrations of sunscreen active ingredients when used in combination. One comment (Ref. 15) submitted in vitro SPF testing data for several different combinations. Although these data showed a statistically significant increased efficacy for lower than minimum concentrations, they were not predictive of the SPF values that would be obtained with human testing and, therefore, were not used to support lower concentrations of sunscreen active ingredients when used in combination. The other comment (Ref. 16) submitted in vivo SPF testing data conducted according to the procedure proposed in the tentative final monograph (58 FR 28194 at 28298 to 28301) in which a selected cross section of active ingredients were tested in pairs by substituting water or the solvent system for the active ingredients. The data were evaluated using a matched pairs comparison statistical hypothesis test procedure and demonstrated that concentrations of sunscreen active ingredients lower than the minimum concentrations proposed in § 352.20(a)(2) for combination products can provide a significant contribution to product effectiveness.

The agency recognizes that technological advances in sunscreen formulation technology since 1978 have resulted in the ability to formulate products with lower concentrations of active

ingredients and higher SPF values. The agency also recognizes that final product testing, and not the concentration of the active ingredients in the combination, ensures product effectiveness.

Due to the recent advances in sunscreen formulation and the data referenced previously, the agency is concerned that setting minimum concentration requirements for active ingredients in sunscreen combination drug products could subject consumers to unnecessary levels of active ingredients. Therefore, the agency is only requiring the maximum concentration limits in § 352.10 for sunscreen active ingredients when used in combination with another sunscreen or when the combination is used with any other permitted active ingredient. However, any such ingredient used in combination with one or more sunscreen active ingredients must be consistent with the regulations in § 330.10(a)(4)(iv), i.e., each of the combined active ingredients must make a contribution to the claimed effect, the combining of active ingredients must not decrease the safety or effectiveness of any individual active ingredient, and the combination must provide rational concurrent therapy for a significant proportion of the target population. Although the agency needs assurance that each ingredient is contributing to the effectiveness of the product, it does not want to impose unnecessary testing requirements on sunscreen product manufacturers. Therefore, the agency is removing the minimum concentration requirement for sunscreen active ingredients proposed in § 352.20 and is adding the requirement that: (1) The concentration of each active sunscreen ingredient used in a combination product must be sufficient to contribute a minimum SPF of not less than 2 to the finished product, and (2) the finished product must have a minimum SPF of not less than the number of the sunscreen active ingredients used in combination multiplied by 2.

E. Comments on Labeling and Testing Procedures for UVA Sunscreen Drug Products

22. In the sunscreen tentative final monograph (58 FR 28194 at 28232 and 28233), the agency proposed to allow claims relating to ''broad spectrum protection'' or ''UVA radiation protection'' for sunscreen products: (1) Containing sunscreen active ingredients with absorption spectra extending to 360 nm or above, and (2) that demonstrate meaningful UVA radiation protection

using appropriate testing procedures to be developed. The agency received numerous comments concerning such claims and current scientific evidence implicates UVA radiation as a major cause of, among other things, photoaging of the skin (Refs. 17 through 20).

In the **Federal Register** of September 16, 1996, and October 22, 1998, the agency proposed a specific skin damage and premature skin aging claim for sunscreen products containing specific concentrations of avobenzone or zinc oxide based upon the submission of data to support claims of UVA radiation protection in such products. The agency will address comments pertaining to measurement of UVA radiation protection in sunscreen products and related UVA radiation protection claims in a future issue of the **Federal Register**. Until then, UVA labeling may continue in accord with the tentative final monograph and its amendments.

F. General Comments on the Labeling of Sunscreen Drug Products

23. Several comments requested that products containing sunscreen ingredients as an adjunct to their main purpose (e.g., a daily moisturizer or a lipstick with a sunscreen) be considered ''secondary sunscreens'' (intended only for incidental or casual sun exposure), and should be subject to different labeling requirements from ''primary'' sunscreen products. A number of comments likewise contended that some of the labeling requirements for ''beach'' or ''primary'' sunscreen products are not appropriate for ''non-beach'' or ''secondary'' sunscreen products.

For example, the comments stated that neither the proposed ''Recommended Sunscreen Product Guide'' nor any other references to sunburn or sunburn protection should be required for secondary sunscreens. Some suggested that the warnings be reduced for secondary sunscreens to a statement such as ''For external use only, keep out of eyes. Discontinue use if signs of irritation appear.'' One comment recommended that the statement of identity for a secondary sunscreen should be its cosmetic function, e.g., ''moisturizer.'' Another recommended stating the primary (cosmetic) function first, then the secondary (drug) function, e.g., ''moisturizing face cream with sunscreen (or with SPF ____ sunscreen).''

The comments also suggested that secondary products be permitted to bear certain labeling claims relating to aging, such as ''Helps reduce the chance of skin aging caused by incidental (or casual) exposure to the sun,'' or ''Helps reduce premature aging from incidental (or casual) exposure to the sun.'' Some also requested the option of being allowed to relate skin aging claims directly to sun exposure, to inform consumers more clearly that sun protection is not the primary attribute of the product, e.g., ''Provides moisture to facial skin throughout the day while protecting facial skin from skin aging due to exposure to sun.'' Other comments recommended that the proposed ''Sun alert'' statement or other references to ''skin cancer'' or other cancers should not be required for secondary products.

On the other hand, the agency also received comments opposing the idea of recognizing ''primary'' and ''secondary'' or ''beach'' and ''non-beach'' categories of sunscreen products. One comment stated that any product containing a sunscreen for the purpose of protection from the sun's harmful effects should be held to the same standards as other sunscreen products. Another comment disagreed with the idea of allowing different sets of claims for ''primary'' and ''secondary'' products. According to this comment, claims such as ''Helps reduce the chance of skin aging'' are drug claims and should be regulated as such. Finally, one comment stated that any sunscreen product (primary or secondary) must have an SPF of 15 to 30 or higher to provide adequate protection, whether for continuous beach exposure or everyday (incidental) sun exposure.

The agency agrees that all sunscreen products (whether drug only or drug-cosmetic) should be held to the same standards (e.g., active ingredient(s), testing requirements, and labeling). Regardless of what type of product a consumer chooses for sun protection, the essential information relevant to sun protection is the same. Thus, to ensure that consumers are adequately protected from overexposure to the sun, all products intended for use as sunscreens should have similar labeling requirements, irrespective of their method of use and irrespective of whether the sunscreen use is considered primary or secondary to the product. Consistent with this approach, the agency

has developed uniform, streamlined labeling for all sunscreen products (see sections II.I through II.L of this document).

The agency also notes, however, that a number of the labeling issues raised in these comments, including the issue of the ''Recommended Sunscreen Product Guide,'' are addressed elsewhere in this document. In addressing these issues, the agency gave careful consideration to the wide variety of products marketed for sunscreen uses.

Finally, the agency notes that under the recently issued standardized OTC drug product labeling format (§ 201.66 (21 CFR 201.66)), manufacturers will not be allowed to commingle drug and cosmetic claims within the ''Drug Facts'' portion of the labeling.

24. One comment requested clarification of the agency's discussion of the term ''anti-aging'' as a claim or as part of a trade name (58 FR 28194 at 28287). The comment was concerned that products containing no sunscreen active ingredients and no sunscreen claims, but which are sold under ''anti-aging'' trade names, would be subject to regulation under the OTC drug sunscreen monograph.

The use of ''anti-aging'' language in a product that made no sunscreen claims and contained no sunscreen active ingredients would not, as the comment asked, cause the product to fall within the scope of the OTC sunscreen drug monograph. Such a product may, however, be subject to regulation as a drug and as a new drug, under section 201(g)(1) and (p) of the act, or as a cosmetic under section 201(i), or as both a drug and a cosmetic, depending upon all of the circumstances surrounding its distribution. A product that is marketed under the final OTC sunscreen drug monograph, but which uses anti-aging language in the labeling to suggest or imply an unapproved therapeutic or physiologic effect, would likely be subject to regulatory action as an unapproved new drug (58 FR 28194 at 28286 to 28287; see comments 37 and 38 in section II.I of this document).

25. Three comments contended that the terms ''natural,'' ''non-chemical,'' and ''chemical free'' are false and misleading in the labeling of OTC sunscreen drug products. The comments

requested the agency to restrict the use of these terms, especially for sunscreen products containing titanium dioxide and zinc oxide.

Generally, the appropriateness of these terms requires case-specific analysis to determine whether their use would render the product false or misleading in any particular (see sections 502(a) and 602(a) of the act). The agency notes, however, that the use of the terms ''non-chemical'' and ''chemical-free'' in the labeling of an OTC sunscreen drug product, to describe the ingredients contained in the product, is likely to be considered unacceptable. Sunscreen drug products contain active (and often inactive) ingredients that have been obtained through a chemical process, or that have been formulated into the finished product through a chemical process. The term ''natural'' is more likely to require context-specific analysis, particularly when used in labeling to describe certain cosmetic aspects or uses of a sunscreen product. The term ''natural,'' however, would not be permitted to appear within the required OTC drug labeling of a sunscreen product and is not considered to be interchangeable with any of the final sunscreen monograph language.

26. Four comments opposed any labeling that a sunscreen product ''does not provide UVA protection,'' contending that FDA's policy does not require disclaimers of broader purposes for which products are not useful. One comment added that an SPF 15 product must block UVA radiation to be effective in preventing sunburn.

Two comments argued that a ''negative warning'' would be useful and necessary to warn and protect consumers and suggested ''Does not provide broad spectrum UVA protection,'' or ''Caution: This product does not provide protection from the recognized dangers of UVA rays which may contribute to skin cancer and other chronic skin disease.''

Labeling should primarily direct consumers towards the purposes for which a product is considered useful. However, in establishing the conditions for the safe and effective use of an OTC drug product, the agency also must take into account, among other things, the context in which a product is customarily marketed and the potential that consumers may use the product

for a use for which it may not be beneficial (see sections 201(n) and 502(a) of the act; § 330.10(a)(3)).

With these factors in mind, the agency will further evaluate whether ''negative warnings'' or disclosure statements are needed when it completes the UVA portion of the sunscreen monograph in a future issue of the **Federal Register**.

27. Four comments contended that the signal words ''Indications'' and ''Directions'' are not needed, take up valuable label space, and should either not be required or be optional, especially for sunscreen-containing drug products that have some ''traditional'' cosmetic uses (e.g., lipsticks).

The agency allows the signal word ''Use'' or ''Uses'' in place of ''Indication'' or ''Indications.'' This short signal word is useful for consumers, appropriate for dual use products, and does not clutter label space. Likewise, the agency concludes that the signal word ''Directions'' is useful for consumers and does not clutter label space (64 FR 13254 at 13264 to 13268, March 17, 1999). The agency is including § 352.52(f) in this final monograph to provide labeling modifications for sunscreen products that meet the small package specifications in § 201.66(d)(10) and are labeled for use on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes). These products include many traditional cosmetics (e.g., lipstick or eye makeup) that may contain sunscreens. These products will be allowed to present a condensed ''Uses'' section and may omit directions for use if they are marketed in a lipstick form.

28. One comment requested that the monograph include professional labeling for both UVB and UVA radiation protection to assist health professionals to select appropriate products. The comment recommended inclusion of the absorption spectrum of each sunscreen in the product and suggested that the labeling include information that the product: (1) Protects against drug-induced photosensitization reactions induced by UV radiation in the ranges ____ nm to ____ nm, and (2) other truthful and nonmisleading statements describing both UVB and UVA radiation protection against photosensitization reactions.

The agency did not propose professional labeling in the tentative final monograph, but did ask for data to be submitted (58 FR 28194 at 28210 and 28245). No data were received. The agency will consider including this type of professional labeling in the monograph in the future when specific supportive data are provided.

G. Comments on Sunscreen Drug Products With High SPF Values

29. Numerous comments objected to the proposed maximum SPF value of 30 for OTC sunscreen drug products. The comments requested either that the agency adopt no limit or a limit of SPF 50, for the following reasons: (1) UV radiation exposure is increasing due to both lifestyle changes and depletion of the atmospheric ozone layer, (2) skin cancer rates are increasing and there is no safe threshold to prevent cancer, (3) people using an SPF 30 sunscreen will have slight sunburn after receiving their 30 MED and therefore should have available sunscreens with higher SPF values, (4) high SPF sunscreens are needed for extremely sun-sensitive people during periods of unavoidable intense or lengthy sun exposure, and because of less than ideal usage by consumers due to misjudging of their skin type and/or inadequate/infrequent application, (5) there is a significant variation of skin types, sensitivities, and UV radiation exposures among people, (6) formulation techniques can increase SPF values without necessarily increasing ingredient concentrations, (7) current information does not support an association between high SPF products and safety concerns, and (8) high SPF products provide for greater relative exposure times and decreased UV radiation transmission. Three comments (Refs. 21, 22, and 23) submitted supporting data.

Some comments stated that "High SPF" (i.e., above SPF 30) products are on the market and used by consumers, and that limiting SPF values would stifle sunscreen product development and preventative health benefits. Other comments argued that sunscreens with high SPF values provide increased protection from ultraviolet radiation effects such as photoimmunosuppression and are needed by those with "dermatological problems."

In contrast, some comments supported the agency's proposal to limit SPF values to 30 to stop the promotional ''bidding war'' or ''horsepower race.'' Another comment contended that real consumer benefit is achieved through appropriate balance of SPF, substantivity, UVA radiation protection, irritation potential, and cost, whereas SPF values above 30 provide only ''incremental benefit'' and an unnecessary increase in drug exposure.

The data provided by the comments in support of allowing numerical values above 30 were of only limited use. Data from a field survey of 62 sunbathers on Miami's South Beach during July 1993 (Ref. 21) did not provide any reliable conclusions on the frequency or extent of solar overexposure by light-skinned individuals or a benefit provided by sunscreen products with an SPF value above 30 as: (1) The sample size was small and the survey population did not represent a random sample, (2) the MED was not determined under controlled conditions or standardized procedure, and (3) full-day UVB radiation exposure was based on crude extrapolation of weather data.

Data from MED determinations on 1,332 people with skin types I, II, and III, and UV radiation data for the month of June 1974 in 5 cities in the United States (Ref. 22), support the contention that a sizeable population may exist that is at risk to more than 30 MED's of UV radiation per day. However, the data are insufficient for extrapolation to the general population. The small sample size in this study limits the sensitivity of the study and the study population did not represent a random sample.

Finally, data from animal studies (Ref. 23) showed that: (1) Limiting sunscreen protection to SPF 30 may not be prudent if UV radiation damage is not related to SPF; (2) a greater amount of sunscreen is needed to completely inhibit some of the nonerythemogenic damage caused by UV radiation, and (3) nonerythemogenic effects (e.g., photoimmunosuppression) occur with suberythemal doses of UV radiation (as can be obtained with the use of low or high SPF sunscreens). While the agency agrees that higher SPF values may provide for greater relative exposure times, the SPF test is not the appropriate measurement of protection from

nonerythemogenic damage because SPF is only a measure of erythema. The agency finds that the data from these studies were not sufficient to either support or dismiss limiting the maximum SPF value in this final rule.

The agency continues to agree with the comments about overall increases in both UV radiation exposure (58 FR 28194 at 28223), skin cancer rates (58 FR 28194 at 28227), and the variation of skin types, sensitivities, and UV radiation exposures among people (58 FR 28194 at 28222). The agency also agrees with the comment that a person using an SPF 30 sunscreen could have a slight sunburn after being exposed to their 30 MED (i.e., after their skin receives a MED). However, the agency continues to believe that an SPF 30 sunscreen product provides adequate protection for the majority of consumers even under extreme conditions, less than ideal usage, or in varying weather conditions (58 FR 28194 at 28225).

On the other hand, the agency is also aware that many OTC sunscreen products with SPF values above 30 are currently marketed and are increasingly used by consumers. Numerous comments from health professionals, consumers, and industry provide actual use information in support of SPF values above 30 for what may be a substantial number of sun-sensitive people in this country. Further, as numerous comments noted: (1) There is a lack of data to correlate higher than SPF 30 sunscreen products with corresponding safety problems, and (2) modern formulation techniques have resulted in higher SPF values using lower active ingredient concentrations.

Because of the numerous concerns from health professionals, new data to support the need for SPF values above 30, and the lack of data concerning safety problems with such SPF values, the agency concludes that OTC sunscreen drug products with SPF values above 30 should be available for those sun-sensitive consumers who require such products based upon personal knowledge of their skin's susceptibility to sunburn, experience with specific products, planned sun exposure, or the recommendation of a health professional. The agency agrees with the comments that higher SPF values generally can provide for greater relative exposure times and decreased

UV radiation transmission. However, the agency continues to believe that the additional sunburn protection provided by an SPF 30 sunscreen and, e.g., an SPF 50 sunscreen (i.e., about a 1.3 percent increase in absorption of erythemal UV radiation) is extremely small for most people. The agency is also concerned about the ability of current testing methods to accurately and reproducibly determine SPF values for high SPF products (see section II.M, comment 53 of this document). In addition, nonlinearity of the SPF rating system is a concept difficult to explain in the limited space on a product label. Therefore, the agency concludes that the label SPF declaration for sunscreens with SPF values above 30 should be limited to one collective term, which appears in § 352.50(a) of this document as follows: ''*For products with SPF values over 30.* ''SPF 30'' (select one of the following: ''plus'' or ''+''). Any statement accompanying the marketed product that states a specific SPF value above 30 or similar language indicating a person can stay in the sun more than 30 times longer than without sunscreen will cause the product to be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act).''

Numerous comments from dermatologists asked that a specific SPF 50 product be allowed to remain on the market because it is needed for the ''ultrasensitive patient'' and for patients with ''dermatological problems.'' The agency has previously discussed the use of high SPF sunscreen drug products to protect consumers with photosensitivity diseases (58 FR 28194 28225) and the need to provide data for such uses (see section II.F, comment 28 of this document) as the absorption spectrum of a specific product, not necessarily the SPF, may be the more clinically significant factor for such people.

As discussed previously in this comment 29 of section II.G of this document, the agency has concluded that the use of SPF label values above 30 in OTC drug products is not supported at this time. The agency, however, invites interested persons to continue developing the test methods needed to measure high SPF values, and to submit the data in support of such methods to FDA. If test methods are developed, the agency also invites interested persons to consider proposed methods for communicating in labeling the level of protection associated with high SPF

values (given the nonlinear nature of the SPF rating system). These and other well-supported improvements to the methodology for accurately and reproducibly measuring SPF values will be addressed, as appropriate, in future issues of the **Federal Register**. Until then, OTC sunscreen drug products are permitted to be labeled with SPF values no higher than ''30+'' or ''30 plus.''

Finally, the agency does not agree with the argument that limiting SPF values would stifle sunscreen product development and preventative health benefits. Undue emphasis for sunburn protection should not be placed upon SPF value alone (i.e., ''single focus products''). As noted by another comment, consumer benefit is achieved through appropriate balance of several factors, including substantivity, UVA radiation protection, and irritation potential.

H. Comments on Water Resistant Labeling and Testing for Sunscreen Drug Products

30. One comment agreed and several disagreed with proposed § 352.52(e)(2)(iii) and (e)(3)(iii) concerning sweat resistant claims based upon water resistance testing instead of a specific sweat resistance test. One comment submitted data from two sweat resistance studies and two water resistance studies (Ref. 24) utilizing methods proposed by the Panel in the ANPRM (43 FR 38206) and involving a total of 117 subjects. The comment concluded that the water resistance test is less stressful than the sweat resistance test.

The agency does not find the data submitted in the studies sufficient to support the comment's contention. The studies each comprised distinct subject populations and addressed a single variable, i.e., the effect of water exposure or induced sweating on a product's SPF. Therefore, a comparison of mean SPF values across studies is not the appropriate measure of relative ''stress'' associated with these variables. The agency believes that a randomized, two-period crossover study design in a single patient population would better have addressed the comment's contention. Further, the Panel's sweat and water resistance protocols provide qualitative information and were not designed to provide comparative assertions requiring valid statistical inferences. Thus, the agency is allowing water and sweat resistant claims based upon the water resistance test procedures in § 352.76 of this document.

31. One comment contended that the ''water resistant'' labeling proposed in § 352.50(b)(1) and (c)(1) should not be required for products labeled or purchased for uses other than swimming or bathing.

The agency notes that the water resistance statements referenced by the comment were not required unless the manufacturer wished to make water resistant claims in the labeling of its sunscreen products. This final rule also will not require a manufacturer to make a water resistance claim for its sunscreen product, even if the product is determined to be water resistant. However, a manufacturer wishing to make water resistance claims must comply with §§ 352.50(b) or (c) and 352.52(b)(1)(ii) or (b)(1)(iii) of this document, as applicable for ''water resistant'' or ''very water resistant'' products.

32. Several comments urged the agency to return to the ''waterproof'' and ''water resistant'' label claims proposed by the Panel and to limit the labeled SPF value to only the SPF after water resistance testing. Another comment requested only general guidelines for claims such as ''water resistant'' or ''sweat resistant'' on the basis that such claims reflect the inherent characteristics of specific formulations and not sunscreen ingredients.

The agency thoroughly discussed use of the terms ''waterproof'' and ''water resistant'' in the tentative final monograph (58 FR 28194 at 28228). The comments did not present any arguments or data that the agency did not previously consider. In addition, the agency points out that performance claims such as these for OTC sunscreen drug products are based on final product formulation.

The agency agrees with the comments that the more relevant SPF value for products labeled ''water resistant'' or ''very water resistant'' is the SPF value of the final product formulation following water resistance testing. Therefore, in this document the agency is limiting the SPF label declaration to the SPF after water resistance testing and is modifying the testing procedures in § 352.76 to reflect deletion of the proposed dual SPF testing requirement for sunscreen products with water resistant claims.

33. Two comments suggested that ''water resistant'' labeling be permitted for drug products retaining at least 80 percent of their SPF value after static testing in pools and that any product meeting this criterion could also be labeled ''sweat proof.'' The comments further suggested that the term ''very water resistant'' should be permitted for products retaining 90 to 98 percent of their SPF after testing.

The agency disagrees with the comments. Simple immersion provides neither an aqueous shear stress nor thermal challenge, and thus is an inadequate assessment of water resistance. In addition, no justification was offered for the respective threshold values of 80 percent and 90 to 98 percent.

34. Several comments contended that the water resistance testing procedures in § 352.76 should be amended to allow for continuation of the water exposure regimen beyond the 80 minute total and suggested that the ''very water resistant'' claim be expanded beyond 80 minutes for products meeting such testing requirements. One comment provided data (Ref. 24) to support extended water resistance claims. Another comment also proposed a testing protocol (Ref. 25) for an additional claim of ''rubproof'' or ''abrasion proof.''

The agency does not concur with an expansion of the ''very water resistant'' claim. Although data submitted by the comment (Ref. 24) show that under testing conditions products may retain their SPF values for up to 270 minutes of water exposure, no usage data were presented to refute the Panel's determination of an 80 minute upper exposure limit (58 FR 28194 at 28277). In addition, the agency believes that for consumers to compare products with multiple performance characteristics, a labeling claim of ''very water resistant'' is best supported by a uniform testing standard. Should the agency receive data in the future indicating customary usage patterns in excess of 80 minutes of water exposure, it will reconsider this limit.

35. One comment disagreed with the agency's proposal in the tentative final monograph (58 FR 28194 at 28278) that manufacturers determine the waiting periods for the most effective use of their sunscreen products (i.e., the time between application and exposure to the sun or water, if applicable). This information would then be included in the directions for the product. The

comment asserted there is no reason to require a "time versus efficacy" study for every sunscreen formula because studies show that products maintain their efficacy for up to 8 hours.

In the tentative final monograph, the agency did not propose a specific method or testing procedure for the determination of a proper waiting period because of the variation in sunscreen product dosage forms and formulations. Instead, the agency allowed manufacturers to make this determination. However, the agency did propose in § 352.52(d)(2) that a waiting period before sun or water exposure, if applicable, be included in the labeling of sunscreen products for their most effective use. In this final rule, the agency has included the requirement for a waiting period in the sunscreen product application statement in proposed § 352.52(d)(1) for the reasons stated in the tentative final monograph (58 FR 28278). The agency continues to allow the manufacturer to determine both the necessity for this statement (based on the product's formulation and dosage form) and how the waiting period, if applicable, is determined.

I. Comments on Indications for Sunscreen Drug Products

36. One comment urged the agency to more strongly state the effectiveness of sunscreens (a specific claim was not suggested). The comment cited a controlled study of a broad spectrum, SPF 17 sunscreen on 431 Caucasian subjects over one summer in Australia (Ref. 26). The study showed that the group using the sunscreen had significantly fewer solar keratoses and more remissions than the control group. Another comment expressed concern that use of the term "help prevent skin damage" may mislead consumers to think that these products prevent skin cancer and premature skin aging.

The agency agrees that solar keratoses are a clinical sign of skin damage. However, although sunscreens are associated with a statistically significant decrease in solar keratoses after 1 or 2 years, the solar keratoses reduction in this study was small and neither the clinical nor biological significance of this reduction has been established. Most solar keratoses never become skin cancers and typically resolve spontaneously (Refs. 27 and 28).

Because of the wide variability possible in the formulation of sunscreen products, not all sunscreen products are identical in their UV radiation absorption characteristics. Sunscreen products may contain active ingredients that absorb in different regions of the UVB radiation spectrum (the primary cause of sunburn) or absorb in both the UVB and different regions of the UVA radiation spectrum. Therefore, even the degree/type of UV radiation protection reported in one study using a specific sunscreen formulation may not be relevant to all possible sunscreen products within the scope of this final monograph. Further, the agency does not believe that it is prudent to extrapolate claims for skin cancer or skin aging based upon a test designed to only measure erythema (i.e., the SPF test).

The agency has reviewed information concerning the mechanisms of skin cancers and photoaging. UV radiation appears to have a dual role in the induction of skin cancers as it can cause several varieties of direct DNA damage (Refs. 23 and 29 through 32) plus suppress the immune response to developing skin cancers (Refs. 33 through 37). This immune suppression may be a critical variable as skin cancers, unlike other cancer types, evoke a strong immune response (especially by Langerhans cells and T-lymphocytes) (Ref. 38). In photoaging, there are multiple sites in the skin that can be damaged by UV radiation (Ref. 17). For example, recent studies support the concept that specific UV radiation-induced enzymes (i.e., matrix metalloproteinases) can mediate connective tissue damage and result in the premature aging effects seen in skin exposed to UV radiation (Refs. 19 and 20). These data also suggest that these mechanisms of carcinogenesis and photoaging can occur from doses of UV radiation below that required to produce sunburn (i.e., suberythemal doses). Thus, even if no sunburn has occurred with the use of a sunscreen, the consumer cannot assume that sun-induced skin damage that might contribute to the eventual development of skin cancer or signs of photoaging has not occurred.

The agency agrees with the comment that terms such as ''help prevent skin damage'' may mislead consumers to think that sunscreen use alone will prevent skin cancer and premature skin aging. However, the agency believes that an appropriate statement can be used to inform consumers

that sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects from the sun when used in a regular program that includes limiting sun exposure and wearing protective clothing (see section II.L, comment 51 of this document).

37. Several comments expressed concern that the statements ''Allows you to stay in the sun up to (insert SPF of product up to 30) times longer than without sunscreen protection'' and ''Provides up to (insert SPF of product up to 30) times your natural protection from sunburn'' in proposed § 352.52(b)(1)(iii) and (b)(1)(iv) may mislead consumers as to the amount and degree of protection sunscreen products provide. The comments were concerned that this message will convey a more expansive meaning than intended and that consumers might be misled about how long they can stay in the sun without risking any sun-induced skin injury. One comment expressed additional concern because the SPF value is only a laboratory test of a few minutes duration.

One comment also objected to the unqualified use of terms such as ''shields from,'' ''protects from,'' ''filters'' or ''screens out'' the ''sun's rays,'' ''sun's harsh rays,'' or ''sun's harmful rays'' to ''help prevent skin damage'' proposed in § 352.52(b)(1)(v) and (b)(1)(vi). The comment expressed concern that these unqualified terms could imply complete protection from the sun's harmful rays and may mislead consumers by inducing a false sense of security when using sunscreen products.

As discussed in section II.I, comment 36 of this document, the agency believes that sunscreen use alone will not prevent all of the possible harmful effects due to the sun. Variation between individuals, UV radiation absorption and substantivity of sunscreen products, exposure conditions, and conditions of use cannot promise a precise result for each individual. Thus, the agency agrees that these statements could provide the wrong message and a false sense of security to some consumers. The agency therefore is not including proposed § 352.52(b)(1)(iii) through (b)(1)(vi) in this final rule and considers these and similar statements to be nonmonograph. For the same reasons, the agency also considers extended wear claims concerning a specific number of hours of ''protection'' (or similar terminology) or an absolute claim such as ''all-day protection'' to

be nonmonograph. Instead, the agency is including an accurate, simpler, and less confusing indication statement in this final rule using two bulleted statements under the ''Uses'' heading, as follows: ''[bullet] helps prevent sunburn'' and ''[bullet] higher SPF gives more sunburn protection''.[1]

38. Several comments contended that terms such as ''skin aging,'' ''wrinkling,'' ''premature skin aging,'' or ''photoaging'' should be permitted as indications for sunscreens, especially if protection is provided in the UVA II (320 to 340 nm) radiation region. One comment suggested that a label claim such as ''Helps reduce the chance of skin aging caused by incidental (or casual) exposure to the sun'' may help to further position the product as a cosmetic for consumers. The comment also suggested an indication statement: ''Excessive, chronic sun exposure can lead to premature photoaging of the skin, characterized by drying, wrinkling and thinning of the skin. Regular use of a sunscreen can help protect against this condition.''

The agency discussed the use of terms such as ''skin aging,'' ''wrinkling,'' ''premature skin aging,'' or ''photoaging'' on sunscreen products in the tentative final monograph (58 FR 28194 at 28236 and 28287). As discussed in the response to comments 36 and 37, the agency has determined that the labeling should describe the product's use in preventing sunburn. A more expansive set of indications is currently unsupported. The agency notes, however, that the final ''Sun alert'' statement (discussed in section II.L, comment 51 of this document) does provide the consumer with information about the role of sunscreens in reducing skin aging, in a context that ensures that the information will not be misleading. The agency, however, is continuing to consider whether certain sunscreens may provide protection against photoaging (58 FR at 28287) and has discussed this in tentative final monograph amendments for certain sunscreens containing avobenzone or zinc oxide based upon specific data submitted to the agency (see section II.E, comment 22 of this document). The agency will evaluate this issue further when it completes the UVA portion of the sunscreen monograph, in a future issue of the **Federal Register**.

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[1] See § 201.66(b)(4)

39. Several comments contended that the extensive labeling proposed in the tentative final monograph was excessive. For environmental concerns, the comments objected to the use of extra packaging materials as a method of including added labeling. One comment disagreed with the need for a specific statement of product indications on individual units of non-beach products properly labeled with an SPF value, and cited limitations on labeling space. The comment suggested that manufacturers be given the option to provide off-package information at the point-of-sale rather than be required to place the statement(s) on each individual unit of the product.

To balance the environmental and regulatory concerns, the agency has streamlined labeling in this final monograph by significantly reducing the amount of required labeling and making optional other labeling that was proposed as required in the tentative final monograph. The agency is also including § 352.52(f) in this final monograph to provide for additional labeling accommodations for sunscreen products that meet the small package specifications in § 201.66(d)(10) and are labeled for use on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes) (see section IV, comment 6 of this document).

J. Comments on Warnings for Sunscreen Drug Products

40. One comment asked the agency to permit reduced warning statements for lip balm products containing sunscreens based on their safe market history. The comment argued that lip balms are not applied to the eye area, and thus extensive eye warnings are not required. Two comments cited the long history of safe use of lipstick products containing sunscreens and suggested the reduced warning, "Discontinue use if signs of irritation appear."

The agency discussed its rationale for proposing an eye warning for sunscreen-containing lip balms in comment 52 of the tentative final monograph (58 FR 28194 at 28229 to 28232), noting that some lip balms could be used on other areas of the face. However, the agency has received neither data concerning adverse reactions due to the use of sunscreen-containing lip balms near the eyes, nor information that such products are normally used in the eye area. These products also are consistent with the factors described in the final OTC standardized content and format

labeling rule (64 FR 13254 at 13270) for considering additional labeling modifications. Accordingly, this final monograph allows sunscreen-containing lipsticks to omit the eye warning in proposed § 352.52(c)(1)(i). As discussed in Section II.J, comment 42 of this document, the wording of this warning is modified in this final monograph. For lip balms, the agency expects to adopt the same modification when it issues the final monograph on OTC skin protectant drug products.

The proposed warning in § 352.52(c)(1)(iii) is now stated as a bullet under the "Stop use and ask a doctor if" subheading as follows: "[bullet] rash or irritation develops and lasts." This warning appears in § 352.52(c)(1)(ii) in this document. Finally, lipsticks (and lip balms, which will be addressed in the final monograph on OTC skin protectant drug products) will not be required to bear the "For external use only" warning. Accordingly, in this final monograph, § 352.52(c)(2) allows lipsticks to omit the warning in § 201.66(c)(5)(i).

41. One comment requested that an eye irritancy warning need not be required for products that contain titanium dioxide as the sole active ingredient. The comment stated that titanium dioxide is an inert inorganic oxide (and thus is chemically distinct from all other Category I sunscreen active ingredients, which are organic compounds) and is an FDA approved color additive for the eye area in both drugs and cosmetics. The comment argued that determination of eye irritancy should be based on total product formulation. A second comment concurred that the labeling for inorganic sunscreens, which are not eye irritants, should be differentiated from organic sunscreens, which may be irritants in the eye.

The agency agrees that the eye warning (proposed in § 352.52(c)(1)(ii)) is based on total formulation, not simply presence of an ingredient. The agency's rationale was discussed in comments 52 and 62 of the tentative final monograph (58 FR 28194 at 28229 to 28232 and 28241). Accordingly, this final monograph requires all sunscreen-containing drug products to bear the eye warning in § 352.52(c)(1)(i). Only products formulated as a lipstick (and lip balms, which will be addressed in the final monograph on OTC skin protectant drug products) may omit this warning

(see § 352.52(c)(3) of this document). The agency will consider omitting the eye warning requirement for a particular formulation if data submitted in an NDA deviation (§ 330.11 (21 CFR 330.11)) from the sunscreen monograph demonstrate it is not an eye irritant.

42. One comment suggested restating the proposed warnings in § 352.52(c)(1) more concisely, as follows: ''For external use only. Keep out of eyes. If contact occurs, rinse thoroughly with water. If irritation or rash occurs, discontinue use. Consult a doctor if problem persists.''

Since the tentative final monograph was published, the agency has published a final rule revising the format and content requirements for OTC drug product labeling (64 FR 13254). Section 201.66(c)(5)(i) requires the warning ''For external use only'' for all topical drug products not intended for ingestion. Therefore, it is not necessary to state that warning in this document and the warning in proposed § 352.52(c)(1)(i) is not included in this final monograph. The agency is shortening the proposed warning in § 352.52(c)(1)(ii). This warning appears in § 352.52(c)(1)(i) in this document as a bullet under the ''When using this product'' subheading as follows: ''[bullet] keep out of eyes. Rinse with water to remove.'' The agency is stating the proposed warning in § 352.52(c)(1)(iii) as a bullet under the ''Stop use and ask a doctor if'' subheading as follows: ''[bullet] rash or irritation develops and lasts.'' This warning appears in § 352.52(c)(1)(ii) in this document. Section 201.66(c)(5)(x) requires the ''Keep out of reach of children'' and accidental ingestion warning set forth in 21 CFR 330.1(g) for these products.

43. One comment contended that the proposed warning about swallowing in § 352.52(c)(1)(i) would not be needed for so-called secondary sunscreen products because adults using these products (which, according to the comment, have traditionally been marketed as cosmetics) would know not to ingest them.

As discussed in section II.J, comment 42 of this document, the warning proposed in § 352.52(c)(1)(i) has been superseded by the warning required by § 201.66(c)(5)(i). The new required warning no longer contains the statement about not swallowing the product.

K. Comments on Directions for Sunscreen Drug Products

44. Two comments stated that the proposed directions in § 352.53(d)(4) for lipsticks and make-up preparations are unnecessary because these products are marketed primarily for their cosmetic uses, which are self-evident. One comment contended that it is unlikely that consumers will modify their habits of lipstick application and usage simply because the product contains a sunscreen. The other comment argued that failure to follow directions for these products is unlikely to have serious consequences.

The agency has determined that directions for use in the labeling of lipstick products containing sunscreens would provide minimal benefit to consumers and the omission of a directions statement is not likely to have serious consequences (see section II.J, comment 40 of this document). However, the agency believes that directions would be useful for make-up products containing sunscreens because of the wide variety of make-up products that are available. Therefore, the agency is revising proposed § 352.52(d)(4) to read: "*For products formulated as a lipstick.* The directions in paragraphs (d)(1) and (d)(2) of this section are not required." The agency expects to finalize the same modifications for lip balm products when it finalizes the monograph for OTC skin protectant drug products.

45. Several comments contended that the proposed direction, "Children under 2 years of age should use sunscreen products with a minimum SPF of 4," is misleading and has no scientific basis. Some comments stated that the direction implies that an SPF 4 may be adequate for children and noted that the Skin Cancer Foundation advises use of SPF 15 or higher for both children and adults. The American Academy of Dermatology questioned why children should not have the benefit of a more highly protective sunscreen. Other comments suggested that this direction should only be required for products with an SPF lower than 4 because it would be nonsensical and a waste of label space on products with higher SPF values.

The agency agrees with the comments that this direction could mislead parents into believing SPF 4 is adequate for children under 2 years of age. Therefore, the agency concludes it is not appropriate and is not including it in § 352.52(d) in this document.

46. One comment stated that the words, ''adults and children 6 months of age and over'' in proposed § 352.52(d)(1) are unnecessary because there is a separate statement, ''Children under 6 months of age: consult a doctor.'' Another comment suggested that lengthy directions for use by children 6 months to 2 years of age are not appropriate for many product types (e.g., a daily facial moisturizer with a sunscreen) and should be revised to ''For adult use only.'' Another comment added that when ''For adult use only'' is used, then warning and cautionary statements concerning use by children would not be needed.

The agency agrees with the comment that the statement, ''Children under 6 months of age: consult a doctor,'' provides sufficient information regarding the age limit for use and is retaining it under § 352.52(d) as a bullet with a small modification as follows: ''[bullet] children under 6 months of age: ask a doctor''. Therefore, the agency is removing the phrase, ''Adults and children 6 months of age and over.'' The proposed directions for children 6 months to 2 years of age referred to by the comments in § 352.52(d)(1), (d)(2), (d)(3), and (d)(5) stated: ''Children under 2 years of age should use sunscreen products with a minimum SPF of 4.'' As discussed in section II.K, comment 45 of this document, the agency concluded that this direction was misleading and did not include it in § 352.52(d) in this document. The agency finds it unnecessary to include the direction ''For adult use only'' in this document because there are only two age groups in the directions: Children under 6 months of age and all other users of the product.

47. One comment argued that the direction ''apply generously'' may be responsible for some skin irritation complaints from consumers. However, the comment did not provide data to support its position. The comment contended that application of smaller amounts of sunscreen may provide adequate coverage, but that in the case of sun protection, it may be best to err on the generous side. Another comment maintained that applying too little sunscreen may significantly lower

protection in a geometric rather than a linear fashion, e.g., an SPF 25 sunscreen applied half as thick as the amount applied for the SPF test may only have the effect of SPF 8.

The agency agrees with the comments that adequate sunscreen should be applied to achieve full labeled SPF protection. Therefore, the agency concludes that the directions in § 352.52(d)(1) of this final monograph to apply ''liberally'' or ''generously'' convey the appropriate message to ensure that consumers adequately apply the sunscreen.

48. One comment stated that the agency should permit firms to provide reapplication instructions based on substantiation information the firm possesses. The comment noted that some products may not need to be applied as frequently as some select time period.

The agency is including a general reapplication direction in § 352.52(d)(2). Manufacturers who have data to support reapplication instructions based on specific substantiation information may submit that information for approval via an NDA deviation as provided in § 330.11.

L. Comments on Product Performance Statements for Sunscreen Drug Products

49. Several comments recommended revisions to proposed § 352.52(e), the statement on product performance. For example, some comments suggested that multiple superlative category designations (e.g., ''high,'' ''very high,'' and ''ultra high'') may foster consumer confusion about the level of protection each SPF provides. Other comments stated that the current SPF scale does not encourage consumers to use higher SPF products. Other comments disagreed with the indication ''permits no tanning.''

The agency has revised proposed § 352.52(e) in this document by condensing the five proposed product categories to three broader ones, and has generalized the category designations. The new categories are: minimal sunburn protection for products with SPF 2 to under 12; Moderate sunburn protection for products with SPF 12 to under 30; high sunburn protection for products with SPF 30 or above. These product category designations (PCD) should appear under the ''Other information'' heading and may also appear on the PDP. Further, products are now described as

providing minimal, moderate, or high protection against tanning, thus deleting the reference to tanning prevention that was proposed in § 352.52(b)(2)(v)(B).

50. Many comments opposed the ''recommended sunscreen product guide'' in proposed § 352.52(e)(4). Some comments noted that the guide is incomplete because it only considers skin type and not duration of exposure, season, geographic location, and other factors that influence choice of product. Other comments stated that the guide is deceptive and may encourage inappropriate use of lower SPF's for protection. Several comments stated that labeling for many products is too small to accommodate the guide. Other comments suggested that information in the guide should be disseminated to consumers through point of sale, television, and weather programs, rather than being required in product labeling.

The agency recognizes that various factors influence the purchase of a sunscreen product, including skin type, geographic location, hours exposed to the sun, and sun reflections. While the product guide was intended as a general guidance for using these products, the agency acknowledges that the guide is incomplete and could be confusing and misleading to consumers. Accordingly, the agency is not including the recommended sunscreen product guide in this document.

51. Many comments requested that the ''Sun alert'' in proposed § 352.52(e)(6) be voluntary instead of required labeling and suggested this information could better be disseminated at the point of purchase or through consumer education programs. Some comments stated that the ''Sun alert'' is too weak and suggested alternate language. One comment observed that the ''Sun alert'' fails to warn consumers that UV radiation may harm the immune system, impairing the body's ability to fight infectious disease. The comment did not provide data to support this claim.

The agency agrees that the ''Sun alert'' should be optional on product labeling. Further, the agency has reevaluated the ''Sun alert'' and concludes that its purpose should be to describe the role of sunscreens in a total program to reduce harmful effects from the sun. Marks (Ref. 39) has noted that sunscreens ''are normally recommended for use as an adjunct to other protection,''

such as clothing, hats, and avoidance of the sun near midday. The agency agrees with this concept, as do many researchers (Ref. 40), the American Academy of Dermatology (Ref. 41), Centers for Disease Control (Ref. 41), and the Governments of Australia and New Zealand (Ref. 42). For this reason, the agency has revised the ''Sun alert'' to include other protective actions consumers can take, and has clarified possible results. The agency is including skin cancer in the ''Sun alert'' instead of the body's ability to fight infectious disease because, to date, skin cancer is the best documented adverse effect of UV radiation on the immune system (Ref. 43). Accordingly, § 352.52(e)(2) in this document provides the following optional ''Sun alert,'' which should appear under the ''Other information'' heading and may also appear on the PDP: ''Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun.'' The agency encourages sunscreen manufacturers to voluntarily include this ''Sun alert'' in the labeling and to otherwise make it available at point of purchase and through consumer education programs.

52. Several comments suggested that the term ''sunblock,'' proposed in the definition in § 352.3(d) and as a labeling statement for products containing titanium dioxide that provide an SPF of 12 to 30 in § 352.52(e)(5), not be included in the final monograph. Some comments argued that the term is unclear and may mislead and confuse consumers into thinking that the product blocks all of the sun, when in fact it does not. One comment stated that no product available totally blocks sun damage. Numerous other comments contended that the term ''sunblock'' should be applied to all sunscreen ingredients that provide an SPF of 12 or higher, as such products block at least 90 percent of the sun's UV rays. One of the comments submitted a study (Ref. 44) to show that micronized titanium dioxide absorbs short wavelength UV radiation and reflects and scatters long wavelengths, thereby functioning similarly to chemical UVB radiation sunscreens. The comment contended that the method in which micronized titanium dioxide performs as a sunscreen active ingredient further justifies the use of the term ''sunblock'' for all sunscreen products with an SPF of 12 or higher.

The agency has decided not to include the term ''sunblock'' in the final monograph and now considers this term nonmonograph. The agency's intention in the tentative final monograph was to provide information to consumers on the method of product performance, not to imply greater protection from using a product labeled as a ''sunblock.'' The agency is concerned that the term ''sunblock'' on the label of sunscreen drug products will be viewed as an absolute term which may mislead or confuse consumers into thinking that the product blocks all light from the sun. For example, consumers might view an SPF 15 product labeled as a sunblock as superior to a product labeled as an SPF 30 broad spectrum sunscreen. As nonmonograph labeling, the term ''sunblock'' cannot appear anywhere in product labeling.

In addition, the proposed definition of ''sunscreen opaque sunblock'' in § 352.3(d) applied only to titanium dioxide and is inconsistent with how micronized titanium dioxide functions as an sunscreen active ingredient (Ref. 44). Further, it is the radiation from the UV portion (290 to 400 nm) of the sun's spectrum that reaches the earth's surface and may produce skin erythema, melanogenesis, and cancer. The agency believes that claims of protection beyond 400 nm (i.e., protection from visible and infra red light) are nonmonograph and not within the scope of this document. Therefore, to provide clear and consistent labeling, the agency is not including proposed §§ 352.3(d) and 352.52(e)(5) in this document.

M. Comments on Testing Procedures for Sunscreen Drug Products

53. Several comments questioned the ability of current testing methods to accurately and reproducibly determine SPF values for high SPF products. Some comments contended that the spectra of currently used solar simulators (especially around 290 nm and above 350 nm) could cause overestimation of SPF for high SPF sunscreens and recommended use of a specifications table that provided percent of erythemal contribution by wavelength regions. Other comments submitted data in support of a high-SPF sunscreen control following concerns expressed by the agency in the proposed rule (58 FR 28194 at 28253 and 28254) that data were not sufficient to demonstrate that the testing methods used to evaluate sunscreen drug products with SPF values

up to 15 are equally applicable to evaluating sunscreen drug products with SPF values above 15. Several comments submitted data and information that questioned the ability of current testing methods to accurately and reproducibly determine SPF values for high SPF products and requested significant changes to proposed subpart D of § 352.70. Other comments requested changes to the testing procedures proposed in subpart D of the sunscreen monograph that were unrelated to products with high SPF values.

The agency believes that the test method proposed in the tentative final monograph (TFM), for measuring SPF values up to 30, represents at this time a straightforward, well-understood, and sound method for measuring these values. The agency therefore is finalizing the method proposed in the TFM. The agency recognizes, however, that testing methods in this area are evolving and that a number of comments raised useful ideas for proposed improvements in the accuracy and reproducibility of the agency's methodology. As discussed in response to comment 29 of section II.G of this document, the agency is also inviting interested persons to continue working on improving SPF testing methods, toward the development of accurate methods for measuring high SPF values. In future issues of the **Federal Register**, if appropriate, the agency will consider proposed improvements to its testing methodology.

54. One comment contended that the calculation of erythema effective exposure (E) serves no practical purpose in the calculation of SPF because the E constant is common to both the numerator and denominator of the equation. Another comment stated that the definition of E is incorrect because it is defined as ''dose'' (Joules/square meter (m^2)) on the left side of the equation $E = \Sigma V_i (\lambda) * I (\lambda)$, whereas the right side of the equation is in terms of irradiance (Watts/m^2). The comment also stated that the unit of time exposure (seconds) is missing on the right side of the equation.

The agency acknowledges that this calculation is not technically necessary if the solar simulator emission spectrum does not change between exposures to protected and unprotected skin.

The same result can then be obtained by measuring the difference (i.e., ratio) in time required to produce erythema on protected versus unprotected skin. However, the agency finds that the calculation of E provides valuable information and is necessary to demonstrate how the MED was determined during SPF testing. The agency agrees with the comment concerning the missing variable of time (in seconds) in the calculation of E and, accordingly, has modified the equation in § 352.73 of this document to read as follows: " $E = \Sigma V_i (\lambda) * I (\lambda) * t_{exp}$"

III. Recent Developments

In the **Federal Register** of October 22, 1998, the agency proposed to amend the tentative final monograph to include zinc oxide as a single ingredient and in combination with any proposed Category I sunscreen active ingredient except avobenzone. Two comments supported the proposal. One comment disagreed with the agency's exclusion of avobenzone from combinations with zinc oxide. Two of the comments urged the agency to expeditiously review and approve a citizen petition (Ref. 45) to recognize this combination.

The agency has informed the petitioner that it is unable to approve the combination without appropriate UVA radiation effectiveness data to demonstrate the UVA radiation protection potential of zinc oxide in combination with avobenzone (Ref. 46). The agency will reconsider this combination for monograph status upon receipt of the appropriate data.

This final rule includes monograph conditions for zinc oxide as a sunscreen active ingredient at concentrations up to 25 percent when used alone or in combination with any monograph sunscreen active ingredient except avobenzone.

IV. Additional Changes

1. The agency has determined that for an active ingredient to be included in an OTC drug final monograph it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. Compendial monographs include an ingredient's official name, chemical formula, and analytical

chemical tests to confirm the quality and purity of the ingredient. These monographs establish public standards for the strength, quality, purity, and packaging of ingredients and drug products available in the United States.

In the **Federal Register** of June 8, 1994, FDA deleted digalloyl trioleate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate, glyceryl aminobenzoate, lawsone with dihydroxyacetone, and red petrolatum from the tentative final monograph due to the lack of interest in establishing USP compendial monographs for these ingredients. Lawsone with dihydroxyacetone subsequently remained under agency consideration due to increased interest by manufacturers in establishing a compendial monograph. Of the 18 remaining sunscreen active ingredients under consideration in the tentative final monograph (58 FR 28194 at 28295, amended at 61 FR 48645 and 63 FR 56584), 16 (aminobenzoic acid, avobenzone, cinoxate, dioxybenzone, homosalate, menthyl anthranilate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, padimate O, phenylbenzimidazole sulfonic acid, sulisobenzone, titanium dioxide, trolamine salicylate, and zinc oxide) currently have compendial monographs. Two (diethanolamine methoxycinnamate and lawsone with dihydroxyacetone) do not have a current or proposed compendial monograph.

The agency is including in § 352.10 of this document the 16 sunscreen active ingredients that currently have a compendial monograph. The agency is reserving the appropriate paragraphs in proposed § 352.10 for the two active ingredients without compendial monographs in case a monograph is developed for either ingredient. Dihydroxyacetone has been proposed for a compendial monograph, but none has been proposed for lawsone. Because these two active ingredients are used in conjunction, lawsone must have a compendial monograph in order for lawsone with dihydroxyacetone to be included in the sunscreen final monograph.

2. The agency has revised proposed § 352.52(b) in response to comments requesting reduction, streamlining, and flexibility of sunscreen labeling and in accordance with new data reviewed by the agency (see section II.I of this document). The agency has revised proposed § 352.52(b)(1) by: (1) Deleting references to any other indication except that pertaining to the prevention of

sunburn (see section II.I, comment 37 of this document), (2) adding (in § 352.52(b)(2) of this final rule) guidance on SPF selection due to simplification of the PCD in proposed § 352.52(e)(1) and deletion of the Recommended Product Guide in proposed § 352.52(e)(4) (see section II.L, comments 49 and 50 of this document), and (3) deleting the quantitative claims (i.e., ''up to (insert SPF of product up to 30) times'') and terms such as ''screens,'' ''shields,'' etc., concerning sunburn protection throughout proposed § 352.52(b) (see section II.I, comment 37 of this document).

3. The tentative final monograph allowed reduced labeling directions on sunscreen products if formulated as a make-up preparation, lipstick, lip balm, or skin preparation and labeled with claims relating only to the prevention of ''lip damage,'' ''freckling,'' or ''uneven coloration.'' Because there is no convincing evidence that SPF testing predicts protection from anything but sunburn (see section II.I, comment 36 of this document), the agency is not including proposed § 352.52(b)(1)(v), (b)(1)(vi), (d)(4), and (d)(5) in this document. The agency will consider including such claims in the monograph when specific supportive data are provided or a specific clinically relevant final formulation test is developed.

4. Numerous comments requested deletion of the dual SPF testing of water resistant products in proposed § 352.50(b)(2) and (c)(2). The agency agrees with the comments (see section II.H, comment 32 of this document) and has revised proposed §§ 352.50(b)(2) and (c)(2) and 352.76 to require only the SPF value after water resistant testing. Further, the agency has modified and made optional the reapplication directions in proposed §§ 352.52(d)(1) and (d)(2) (see section II.K, comment 48 of this document). These changes to proposed § 352.52(d) provide flexibility by allowing manufacturers to expand on reapplication information necessary for specific sunscreen formulations and by equalizing requirements between products with and without water resistance claims and between sunscreen drug and drug-cosmetic products. Thus, the water resistance labeling in § 352.52(b)(1)(ii) and (b)(1)(iii) of this document should also serve as a directive for reapplication of the product. In summary, for products making water and/or sweat resistance claims,

the agency has modified and combined water resistance statements formerly in proposed § 352.52(e)(2), (e)(3), (d)(1), and (d)(2) into § 352.52(b)(1)(ii) and (b)(1)(iii) in this document.

5. The agency has modified references to ''tanning'' and ''prolongs exposure time'' in proposed § 352.52(b)(2) by combining the PCD claim in § 352.52(e)(1) of this document with either the phrase ''protection against sunburn'' or ''protection against sunburn and tanning.'' Based upon current information, the agency believes that the terms proposed in the tentative final monograph could send the wrong message relative to the dangers of even suberythemal UV radiation exposure and give consumers a false sense of security concerning sun exposure and sunscreen use. The agency has reduced and simplified the other optional, additional indications in proposed § 352.52(b)(2) to reflect a modified, simpler, combined version of the PCD in proposed § 352.52(e)(1) (see section II.L, comment 49 of this document) and the ''Recommended Product Guide'' in proposed § 352.52(e)(4) (see section II.L, comment 50 of this document). Because the agency has deleted reference to use of the term ''Sunblock'' in proposed section § 352.52(e)(5) (see section II.L, comment 52 of this document), it has deleted reference to ''Reflects the burning rays of the sun'' in proposed § 352.52(b)(3) for the same reasons.

6. Several comments requested labeling exemptions or flexibility for packages that are too small to accommodate all required information. Some comments specifically requested flexible labeling for products based upon their intended use, such as lipsticks and lip balms.

As discussed in the final rule establishing standardized format and content requirements for the labeling of OTC drug products (64 FR 13254 at 13267 to 13268 and 13289), the agency has established specifications for small packages in § 201.66(d)(10). The agency also stated in the final labeling rule that it will consider additional approaches for accommodating certain small-package products in their respective OTC drug monograph proceedings.

The agency considers the required OTC drug labeling information essential for the safe and effective use of these products and important to consumers for selection of an appropriate product. Nevertheless, the agency agrees that excessive labeling requirements may discourage manufacturers

from marketing certain products, such as lipsticks or lip balms containing sunscreens, which provide significant public health benefit.

In this OTC drug rulemaking, the agency has included several accommodations for products such as lipsticks (and lip balms, which will be addressed in the final monograph on OTC skin protectant drug products), taking into consideration the intended uses of these products, the limited areas to which these products are applied, and the overall safety profile of these products, and other factors described in the final OTC labeling rule (64 FR 13254 at 13270). The agency is including § 352.52(f) in this document to provide for labeling modifications for sunscreen products that meet the small package specifications in § 201.66(d)(10) and are labeled for use on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes).

7. The agency has revised §§ 700.35 and 740.19 (21 CFR 700.35 and 740.19) in response to comments requesting clarification on whether certain products will be subject to regulation as drugs (see section II.B, comments 8 through 11 of this document). Section 700.35 has been revised to make clear that, generally, products that make sun protection claims, whether express or implied, are subject to regulation as drugs. Only those products that contain a sunscreen ingredient solely for a nontherapeutic, nonphysiologic use (e.g., as a color additive, or to protect the color of the product such as in a nail polish or hair coloring product) (see 58 FR at 28205), and which include a labeling statement that accurately describes that use, may be marketed as cosmetic products. Section 740.19 has been revised to make clear that the term ''suntanning preparations'' does not include products intended to provide sun protection or otherwise to affect the structure or any function of the body. Suntanning preparations include gels, creams, liquids, and other topical products that are intended to provide cosmetic effects on the skin while tanning through exposure to UV radiation (e.g., moisturizing or conditioning), or that are intended to give the appearance of a tan by imparting color through the application of approved color additives (e.g., dihydroxyacetone) without the need for exposure to UV radiation (i.e., sunless tanning products).

V. Conclusion

The agency is issuing a final monograph establishing conditions under which OTC sunscreen drug products are generally recognized as safe and effective and not misbranded; 16 ingredients listed in § 352.10 are currently a monograph condition. Any drug product labeled, represented, or promoted for use as an OTC sunscreen drug that contains any of the nonmonograph ingredients listed in § 310.545(a)(29), or that is not in conformance with the monograph (21 CFR part 352), may be considered a new drug within the meaning of section 201(p) of the act and misbranded under section 502 of the act. Such a drug product cannot be marketed for OTC sunscreen use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations. An appropriate citizen petition to amend the monograph may also be submitted in accord with 21 CFR 10.30 and § 330.10(a)(12)(i). The agency will address sunscreen active ingredients that have foreign marketing experience and data at a future time. Any OTC sunscreen drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule for § 310.545(a)(29) or this document that is not in compliance with the regulations is subject to regulatory action.

VI. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP1, Docket No. 78N–0038, Dockets Management Branch.

2. Comment No. CP2, Docket No. 78N–0038, Dockets Management Branch.

3. Comment No. CP3, Docket No. 78N–0038, Dockets Management Branch.

4. Comment No. CP7, Docket No. 78N–0038, Dockets Management Branch.

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21. Comment No. C00282, Docket No. 78N–0038, Dockets Management Branch.

22. Comment No. C00365, Docket No. 78N–0038, Dockets Management Branch.

23. Comment No. C00531, Docket No. 78N–0038, Dockets Management Branch.

24. Comment No. C00128, Docket No. 78N–0038, Dockets Management Branch.

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47. Food and Drug Administration, "Supplement to the Economic Impact Analysis of the Sunscreen Drug Products for Over-the-Counter Human Use; Final Monograph," in OTC Vol. 06FR, Docket No. 78N–0038, Dockets Management Branch.

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VII. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. OMB has determined that the final rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation) (2 U.S.C. 1532).

Because the rule may have a significant economic impact on a substantial number of small entities, this section of the preamble constitutes the agency's Final Regulatory Flexibility Analysis. Because the rule does not impose any mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any 1 year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291, was discussed in the tentative final monograph for OTC sunscreen drug products (58 FR 28194 at 28294). The agency received only one response to the specific request for data and

comment on the economic impact of this rulemaking. This comment discussed the costs that would result from proposed changes in sunscreen product labeling and testing methods. The agency's review of this comment is included as follows.

A. Background

The purpose of this document is to establish conditions under which OTC sunscreen drug products are generally recognized as safe, effective, and not misbranded. The document sets specific requirements for appropriate monograph ingredients, labeling format and content, and SPF value and water resistant testing. Although the agency cannot quantify the overall expected benefits, each provision of the rule will support the ability of consumers to take desired protective actions. Monograph ingredients have been proven safe and effective assuring the quality of sunscreen products. This benefits consumers because it ensures that the product will provide ingredients that safely protect against sunburn. The new product labeling will better inform consumers about the sunburn protection provided by the products; and if manufacturers choose to include the optional ''Sun alert'' labeling statement, the product labeling can reference that the use of sunscreens may reduce the risk of skin aging, skin cancer, and other harmful effects of the sun. These labeling requirements, in conjunction with the format requirements of the OTC uniform labeling rule (64 FR 13254) will provide clearer and more concise information that will benefit consumers in at least four ways: (1) They will increase understanding regarding the selection of sunscreen drug products, (2) they will make product comparison easier, (3) they will enhance the ability to make informed decisions regarding product purchases and proper use, and (4) they will make it easier to distinguish between sunscreen drug products that contain sunscreens and suntanning products that do not. Finally, the new requirements for product testing will assure the accuracy of the SPF value on the product label. By improving the accuracy of these ratings, this requirement will provide further assurance that consumers receive adequate sunburn protection.

The rule will require all manufacturers and distributors (or their agents) to relabel their OTC sunscreen drug products to comply with the monograph language. The labeling of certain

suntanning products that do not contain sunscreens will need to include the new required warning statement. In some cases, the labeling of cosmetics containing sunscreens for nontherapeutic, nonphysiologic uses (e.g., to protect hair from sun damage) will need to describe the cosmetic role of the sunscreen ingredient(s). The SPF of some OTC sunscreen drug products may need to be retested using the method described in the final monograph. In addition, only products containing the active ingredients included in this final rule will be generally recognized as safe, effective, and not misbranded. Of the 18 active ingredients under consideration in the proposed rule, 16 currently have the required USP/N.F. compendial monographs. The USP has not received applications for the remaining two ingredients. If either of these active ingredients are not included in the USP and added to the monograph by (*insert date 24 months after date of publication in the* **Federal Register**), products containing these ingredients would need to be reformulated to replace the nonmonograph ingredient with a monograph ingredient, or the product must be removed from the market.

B. Number of Products Affected

Based on data from FDA's Drug Listing System, the agency estimates that there are approximately 2,800 OTC sunscreen drug products (different formulations, not including products that differ only by color) and about 12,000 individual stockkeeping units (SKU's) (individual products, packages, and sizes). All of the SKU's will need to be relabeled, some will require new SPF testing, and those products lacking approved active ingredients will need to be reformulated to stay on the market.

In addition, certain suntanning products and certain cosmetic products containing sunscreens will have to be relabeled. As FDA's Drug Listing System does not include suntanning products, the agency used 1995 data from A. C. Nielsen, a recognized provider of market data, to estimate that approximately 550 suntanning SKU's will be affected by the labeling requirements of this rule. New labels will also be needed for cosmetic products that contain a sunscreen for a nontherapeutic use and that include the word "sunscreen" or similar terms in product labeling.

The agency is unable to identify the number of these cosmetic products, but does not believe that there are a large number of SKU's in this category.

C. Cost to Relabel

The relabeling costs for this rule will be moderated to the extent that manufacturers coordinate labeling changes for the final sunscreen monograph with labeling changes required by the recent rule establishing uniform format and content for OTC drug product labeling (64 FR 13254). These costs are not discussed in this analysis, however, because they are already accounted for in the agency's analysis of its OTC drug product labeling rule. That is, the agency's economic analysis of that rule excluded redesign costs for all OTC drug products not marketed under current NDA's or current final monographs, explaining that the agency would attribute all redesign costs associated with future final monographs to each final monograph rule as it published. All redesign costs for this final sunscreen monograph therefore are attributed to this rule alone.

Approximately 12,000 sunscreen drug SKU's will have to be relabeled within a 2-year implementation period to comply with the labeling requirements of this final rule. In addition, approximately 550 suntanning SKU's will have to be relabeled within a 12-month implementation period. (As noted previously, FDA could not estimate the number of cosmetic products that contain a sunscreen for a nontherapeutic use and that include the word ''sunscreen'' or similar terms in product labeling. The agency believes, however, the relabeling of this group of cosmetic products will impose a minimal economic burden because some of these products already include the required labeling, and most manufacturers revise these labels for marketing considerations more frequently than the allowed 2-year phase-in period. Therefore, the agency's estimates do not include a cost for relabeling those products that contain sunscreens for a nontherapeutic, nonphysiologic use.)

Frequent labeling redesigns are a recognized cost of doing business in the OTC drug industry, particularly for drug-cosmetic and seasonal products. Thus, SKU's with labels that would normally be redesigned within the implementation periods were assumed to incur no additional costs. The

cost for the remaining SKU's was calculated as the lost value of the remaining life-years of the existing label design. FDA estimates that labeling for the majority (90 percent) of the SKU's affected by this final rule are redesigned at least every 2 years. Of the remaining SKU's, the agency assumes that half would be redesigned every 3 years and half every 6 years. Because the required labeling for OTC sunscreen drug products now includes fewer words than the previous language and the final rule contains a number of labeling modifications for products used on small areas of the face (which are usually marketed in small size packages), this rule is not expected to require manufacturers to increase the package size or available labeling space. (Although costs of redesigning labels for future final monographs were excluded from FDA's analysis of its OTC drug product labeling rule, costs for increased package sizes were considered in the analysis of impacts for that regulation (64 FR 13254 at 13283)).

FDA estimated the cost of redesign by counting only the value of the label-years that would be lost, after adjusting for the length of the traditional labeling cycle. The regulatory cost was calculated as the product of the number of SKU's, the number of years of labeling life lost, and the value of each year of labeling life lost (see 64 FR 13254 at 13278 through 13284).[2]

Table 1 in section VIII.C of this document details FDA's estimates of the distribution of relabeling costs resulting from the final rule. A weighted average cost to redesign a label of $5,210 per SKU was used to calculate the relabeling cost of sunscreen drug products, whereas a weighted

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[2] Mathematically the following formula was used to calculate the incremental relabeling costs:

$Cost_{yx} = \Sigma\, j\, N_x A_x(1/x)$, where j = 1 to (x-y)

Total $Cost_y = Cost_{y6} + Cost_{y3} + Cost_{y2}$

where:

x = life of labeling in years (2, 3, or 6)

y = phase-in period in years

N_x = number of SKU's with labeling life of x years, and

A_x = amortized annual value of labeling with a life of x years.

average cost of $6,620 per SKU was used to calculate the cost of relabeling suntanning products. A detailed description of the cost analysis is on file with the Docket Management Branch (Ref. 47). As shown, the total incremental cost to relabel the approximately 12,000 sunscreen drug SKU's is about $1.5 million, while the cost to relabel the approximately 550 suntanning SKU's was about $1.8 million. The greater per SKU cost for relabeling suntanning products reflects the shorter, 12-month, phase-in period. With a shorter phase-in period, manufacturers are less able to incorporate labeling changes into voluntary redesign cycles and, therefore, lose label inventory.

TABLE 1.—ONE-TIME COST TO RELABEL SUNSCREEN AND SUNTANNING SKU'S ($)

	Type of Product		
Size of Company	Drug	Suntanning	Total Cost
Small[1]	649,283	1,128,700	1,777,983
Large	860,677	691,800	1,552,477
Total Cost	1,509,960	1,820,500	3,330,460

[1] See section VII.G of this document.

The one comment that raised economic issues in response to the tentative final monograph expressed concern about available labeling space on small packages of sunscreen drug products. The comment stated that all text needs to be concise. The agency considered this comment in developing the final rule, which contains specific labeling modifications for small packages and for sunscreen products used on small areas of the face (e.g., lips, nose, ears, and/or around the eyes).

D. Cost to Retest SPF

FDA is uncertain about the number of OTC sunscreen drug products that have not been tested using the monograph SPF test method. However, the SPF test method in this document is essentially the same as the method described in the proposed rule. If manufacturers have added new products, made formulation changes, or otherwise needed to test or retest the SPF of their products since 1993, they would probably have used the most current (i.e., the proposed) test method. Therefore, the agency estimates that from 15 to 30 percent of the sunscreen drug products will require retesting as a result of this document. The cost of the SPF test varies, depending on the product claim (water resistant or very water resistant) and SPF factor tested, and ranges from $2,500 to $6,500.

On the assumption that 50 percent of the traditional sunscreen drug products, and none of the make-up type sunscreen products, make water resistant claims, and 50 percent of the products that make water resistant claims make very water resistant claims, the estimated weighted average cost of the SPF test is $3,514. FDA estimates the total cost of this requirement, therefore, to range from $3.1 million to $6.1 million (see the following Table 2).

TABLE 2.—ONE-TIME COST TO RETEST SPF ASSUMING 15 PERCENT OR 30 PERCENT COMPLIANCE RATES ($)

Size of Company	15 Percent Non-compliance	30 Percent Non-compliance
Small	1,300,000	2,600,000
Large	1,800,000	3,500,000
Total Cost	3,100,000	6,100,000

E. Cost to Reformulate

Reformulation costs will depend on the number of products, if any, that will have no active ingredients with completed USP compendial monographs by the end of the implementation period. At the present time, only two of the active ingredients being considered do not have a USP monograph. According to the agency's drug listing system, two products, manufactured by one company contain one of these ingredients. The agency is not currently aware of other products in the marketplace that contain these two ingredients.

The cost to reformulate a product varies by the nature of the reformulation, the type of product, and the size and complexity of the company. Because OTC sunscreen drug products are well characterized topical formulations, FDA estimates the cost to reformulate at about $350,000 per product. Thus, on the assumption that the manufacturer reformulates rather than removes the products from the market, the one-time cost of reformulation for two products would be $700,000.

F. Total Incremental Costs

The estimated total one-time incremental cost of this rule, using the midpoint of the cost range for retesting and reformulation is $8.6 million (see Table 3 of this document). These estimates are based on 16 of the 18 active sunscreen ingredients under consideration having USP compendial

monographs. If a USP monograph is completed for the one ingredient in these two products or if the two products are removed from the market, the cost of reformulation would be eliminated.

G. Small Business Impact

Based on the analysis of FDA's drug listing system and other data described previously, there are about 180 domestic companies that manufacture OTC sunscreen and suntanning products. Distributors were not assigned costs because manufacturers of OTC drug products are usually responsible for product labeling, testing, and formulation. Approximately 78 percent of these firms meet the Small Business Administration's definition of a small entity for this industry (less than 750 employees).

TABLE 3.—TOTAL INCREMENTAL COST TO INDUSTRY ($)

Size of Company	Relabel Products		Retest SPF[1]	Reformulation[2]	Total
	Drug	Suntanning			
Small	670,000	1,100,000	2,000,000	n/a	n/a
Large	840,000	700,000	2,600,000	n/a	n/a
Total Cost	1,510,000	1,800,000	4,600,000	700,000	8,610,000

[1] Assumes 22.5 percent noncompliance (midpoint of range)
[2] Assumes 2 products would require reformulation

The rule will require manufacturers of sunscreens to relabel their products. Some firms will need to retest the SPF of these products, and one firm may have to reformulate or remove two products from the market. Because of the 2-year implementation period, most firms will be able to relabel during a normal relabeling cycle, at no additional cost. FDA cannot estimate with certainty the number of small firms that will need to retest or reformulate their OTC sunscreen products, but projects that from 15 to 30 percent of all products may need to be retested and that 2 products may need to be reformulated. Costs will vary by firm, depending on the type and number of products requiring relabeling, retesting, and reformulation. The firm-specific impact may vary inversely with the volume of product sales, however, because per unit costs will be lower for products with high volume sales. Thus, the relative economic impact of product retesting or relabeling may be greater for small firms than for large firms.

Because of the 2-year phase-in period allowed for sunscreen drug and drug-cosmetic products, which allows manufacturers the flexibility to incorporate regulatory changes with voluntary/market-driven changes, the economic impact of the relabeling requirement is relatively low (approximately $3.3 million). However, for those small companies that may have to relabel a substantial number of products, the out-of-pocket costs could be significant.

Also, the cost to a small company needing to reformulate a product, estimated at approximately $350,000 would be significant. This impact may be moderated by other options available, which may be more cost effective than reformulation. For example, a manufacturer may be able to substitute other formulations, shift production to a contract manufacturer with an approved formulation, or temporarily remove the product from the market and await the completion of a USP compendial monograph for the ingredient. Because the OTC drug industry is highly regulated, all firms are expected to have access to the necessary professional skills on staff or to make contractual arrangements to comply with the paperwork and other requirements of this rule.

H. Analysis of Alternatives

The agency altered several proposed regulatory provisions to reduce the economic burden of this rule on industry. For example, FDA decreased the amount of required labeling and provided small package accommodations for certain products. The labeling required by the proposed rule would have increased the needed label and/or package size for as many as 90 percent of the sunscreen products. Such size adjustments could have imposed estimated additional one-time relabeling costs of $18 million and annually recurring costs of $22 million (see Eastern Research Group, ''Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Rule'' (Ref. 48)). Also, in response to the comment (see section II.H, comment 32 of this document), the agency has reconsidered its position on SPF testing of water resistant and very water resistant products and eliminated the static test requirement for these products. As the average cost of the static test is approximately $2,800, the estimated savings to industry due to the elimination of this test is about $750,000.

The agency also considered a number of implementation alternatives to this final rule. Generally, the agency allows only a 1-year implementation period for final monographs. However, because most sunscreen products are produced seasonally, the 2-year period will substantially enhance the ability of the industry to relabel and reformulate its products, if necessary, and sell its existing product inventories. The 2-year period will also allow sunscreen manufacturers to coordinate the required labeling changes with routine industry-initiated labeling changes and changes required by the new OTC drug product labeling final rule (64 FR 13254).

A 3-year implementation period for sunscreen drug products was considered, but the agency determined that a 2-year period provides sufficient time to allow the required relabeling and product retesting to be completed. The agency found that the savings to industry of delayed implementation (estimated to be about $845,000) were not great enough to justify delaying appropriate use and safety information to consumers of OTC sunscreen drug products.

Finally, the agency is providing a 12-month implementation period for certain suntanning preparations to add new warning information. For this category, consumers may believe that these products are providing sun protection when, in fact, they do not. They may forego using other products that have been demonstrated to be effective in providing sun protection, believing that their tanning product provides some measure of protection. Because the new warning for suntanning preparations presents an important safety issue that needs to be conveyed to consumers at the earliest possible date, the agency considered requiring a 6-month implementation period for these products. However, given the seasonal nature of these products, the agency was concerned that some manufacturers may not have sufficient time to incorporate the labeling change without disrupting their production schedules. By providing an additional 6 months to implement the change, compliance costs were reduced by $1.8 million.

VIII. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information''

under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq.). Rather, the labeling statements are a ''public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

IX. Environmental Impact

The agency has determined that under 21 CFR 25.31(c) this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 352

Labeling, Over-the-counter drugs.

21 CFR Part 700

Cosmetics, Packaging and containers.

21 CFR Part 740

Cosmetics, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 352 is added and 21 CFR parts 310, 700, and 740 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by adding paragraph (a)(29), by revising paragraph (d) introductory text, by adding and reserving paragraph (d)(30), and by adding paragraph (d)(31) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(29) *Sunscreen drug products.*

Diethanolamine methoxycinnamate

Digalloyl trioleate

Ethyl 4-[bis(hydroxypropyl)] aminobenzoate

Glyceryl aminobenzoate

Lawsone with dihydroxyacetone

Red petrolatum

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(31) of this section.

* * * * *

(30) [Reserved]

(31) (*Insert date 24 months after date of publication in the* **Federal Register**) for products subject to paragraph (a)(29) of this section.

3. Part 352 is added to read as follows:

PART 352—SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

Subpart A—General Provisions

§ 352.1 Scope.

(a) An over-the-counter sunscreen drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 352.3 Definitions.

As used in this part:

(a) *Minimal erythema dose (MED).* The quantity of erythema-effective energy (expressed as Joules per square meter) required to produce the first perceptible, redness reaction with clearly defined borders.

(b) *Product category designation (PCD).* A labeling designation for sunscreen drug products to aid in selecting the type of product best suited to an individual's complexion (pigmentation) and desired response to ultraviolet (UV) radiation.

(1) *Minimal sun protection product.* A sunscreen product that provides a sun protection factor (SPF) value of 2 to under 12.

(2) *Moderate sun protection product.* A sunscreen product that provides an SPF value of 12 to under 30.

(3) *High sun protection product.* A sunscreen product that provides an SPF value of 30 or above.

(c) *Sunscreen active ingredient.* An active ingredient listed in § 352.10 that absorbs, reflects, or scatters radiation in the UV range at wavelengths from 290 to 400 nanometers.

(d) *Sun protection factor (SPF) value.* The UV energy required to produce an MED on protected skin divided by the UV energy required to produce an MED on unprotected skin, which

may also be defined by the following ratio: SPF value = MED (protected skin (PS))/MED (unprotected skin (US)), where MED (PS) is the minimal erythema dose for protected skin after application of 2 milligrams per square centimeter of the final formulation of the sunscreen product, and MED (US) is the minimal erythema dose for unprotected skin, i.e., skin to which no sunscreen product has been applied. In effect, the SPF value is the reciprocal of the effective transmission of the product viewed as a UV radiation filter.

Subpart B—Active Ingredients

§ 352.10 Sunscreen active ingredients.

The active ingredient of the product consists of any of the following, within the concentration specified for each ingredient, and the finished product provides a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part:

(a) Aminobenzoic acid (PABA) up to 15 percent.

(b) Avobenzone up to 3 percent.

(c) Cinoxate up to 3 percent.

(d) [Reserved].

(e) Dioxybenzone up to 3 percent.

(f) Homosalate up to 15 percent.

(g) [Reserved].

(h) Menthyl anthranilate up to 5 percent.

(i) Octocrylene up to 10 percent.

(j) Octyl methoxycinnamate up to 7.5 percent.

(k) Octyl salicylate up to 5 percent.

(l) Oxybenzone up to 6 percent.

(m) Padimate O up to 8 percent.

(n) Phenylbenzimidazole sulfonic acid up to 4 percent.

(o) Sulisobenzone up to 10 percent.

(p) Titanium dioxide up to 25 percent.

(q) Trolamine salicylate up to 12 percent.

(r) Zinc oxide up to 25 percent.

§ 352.20 Permitted combinations of active ingredients.

The SPF of any combination product is measured by the testing procedures established in subpart D of this part.

(a) *Combinations of sunscreen active ingredients.* (1) Two or more sunscreen active ingredients identified in § 352.10(a), (c), (e), (f), and (h) through (r) may be combined with each other in a single product when used in the concentrations established for each ingredient in § 352.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

(2) Two or more sunscreen active ingredients identified in § 352.10(b), (c), (e), (f), (i) through (l), (o), and (q) may be combined with each other in a single product when used in the concentrations established for each ingredient in § 352.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

(b) [Reserved].

(c) [Reserved].

Subpart C—Labeling

§ 352.50 Principal display panel of all sunscreen drug products.

In addition to the statement of identity required in § 352.52, the following labeling statements shall be prominently placed on the principal display panel:

(a) *For products that do not satisfy the water resistant or very water resistant sunscreen product testing procedures in § 352.76.*

(1) *For products with SPF values up to 30.* ''SPF (insert tested SPF value of the product up to 30).''

(2) *For products with SPF values over 30.* ''SPF 30'' (select one of the following: ''plus'' or ''+''). Any statement accompanying the marketed product that states a specific SPF value above 30 or similar language indicating a person can stay in the sun more than 30 times longer than without sunscreen will cause the product to be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act).

(b) *For products that satisfy the water resistant sunscreen product testing procedures in § 352.76.*

(1) (Select one of the following: ''Water,'' ''Water/Sweat,'' or ''Water/Perspiration'') ''Resistant.''

(2) ''SPF (insert SPF value of the product, as stated in paragraph (a)(1) or (a)(2) of this section, after it has been tested using the water resistant sunscreen product testing procedures in § 352.76).''

(c) *For products that satisfy the very water resistant sunscreen product testing procedures in § 352.76.*

(1) ''Very'' (select one of the following: ''Water,'' ''Water/Sweat,'' or ''Water/Perspiration'') ''Resistant.''

(2) ''SPF (insert SPF value of the product, as stated in paragraph (a)(1) or (a)(2) of this section, after it has been tested using the very water resistant sunscreen product testing procedures in § 352.76).''

§ 352.52 Labeling of sunscreen drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a ''sunscreen.''

(b) *Indications.* The labeling of the product states, under the heading ''Uses,'' all of the phrases listed in paragraph (b)(1) of this section that are applicable to the product and may contain any of the additional phrases listed in paragraph (b)(2) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient in § 352.10.* (i) ''[bullet][1] helps prevent sunburn [bullet] higher SPF gives more sunburn protection''.

(ii) *For products that satisfy the water resistant testing procedures identified in § 352.76.* ''[bullet] retains SPF after 40 minutes of'' (select one or more of the following: ''activity in the water,'' ''sweating,'' or ''perspiring'').

(iii) *For products that satisfy the very water resistant testing procedures identified in § 352.76.* ''[bullet] retains SPF after 80 minutes of'' (select one or more of the following: ''activity in the water,'' ''sweating,'' or ''perspiring'').

(2) *Additional indications.* In addition to the indications provided in paragraph (b)(1) of this section, the following may be used for products containing any ingredient in § 352.10:

(i) *For products that provide an SPF of 2 to under 12.* Select one or both of the following: [''[bullet]'' (select one of the following: ''provides minimal,'' ''provides minimum,'' ''minimal,'' or ''minimum'') ''protection against'' (select one of the following: ''sunburn'' or ''sunburn and tanning'')], or ''[bullet] for skin that sunburns minimally''.

(ii) *For products that provide an SPF of 12 to under 30.* Select one or both of the following: [''[bullet]'' (select one of the following: ''provides moderate'' or ''moderate'') ''protection

[1] See § 201.66(b)(4) of this chapter.

against'' (select one of the following: ''sunburn'' or ''sunburn and tanning'')], or ''[bullet] for skin that sunburns easily''.

(iii) *For products that provide an SPF of 30 or above.* Select one or both of the following: [''[bullet]'' (select one of the following: ''provides high'' or ''high'') ''protection against'' (select one of the following: ''sunburn'' or ''sunburn and tanning'')], or ''[bullet] for skin highly sensitive to sunburn''.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading ''Warnings:''

(1) *For products containing any ingredient in § 352.10.* (i) ''When using this product [bullet] keep out of eyes. Rinse with water to remove.''

(ii) ''Stop use and ask a doctor if [bullet] rash or irritation develops and lasts''.

(2) *For products containing any ingredient identified in § 352.10 marketed as a lipstick.* The external use only warning in § 201.66(c)(5)(i) of this chapter and the warning in paragraph (c)(1)(i) of this section are not required.

(d) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading ''Directions.'' More detailed directions applicable to a particular product formulation (e.g., cream, gel, lotion, oil, spray, etc.) may also be included.

(1) *For products containing any ingredient in § 352.10.* (i) ''[bullet] apply'' (select one or more of the following, as applicable: ''liberally,'' ''generously,'' ''smoothly,'' or ''evenly'') ''(insert appropriate time interval, if a waiting period is needed) before sun exposure and as needed''.

(ii) ''[bullet] children under 6 months of age: ask a doctor''.

(2) *In addition to the directions provided in § 352.52(d)(1), the following may be used for products containing any ingredient in § 352.10.* ''[bullet] reapply as needed or after towel drying, swimming, or'' (select one of the following: ''sweating'' or ''perspiring'').

(3) *If the additional directions provided in § 352.52(d)(2) are used, the phrase ''and as needed'' in § 352.52(d)(1) is not required.*

(4) *For products marketed as a lipstick.* The directions in paragraphs (d)(1) and (d)(2) of this section are not required.

(e) *Statement on product performance*—(1) *For products containing any ingredient identified in § 352.10, the following PCD labeling claims may be used under the heading ''Other information'' or anywhere outside of the ''Drug Facts'' box or enclosure.*

(i) *For products containing active ingredient(s) that provide an SPF value of 2 to under 12.* (Select one of the following: ''minimal'' or ''minimum'') ''sun protection product.''

(ii) *For products containing active ingredient(s) that provide an SPF value of 12 to under 30.* ''moderate sun protection product.''

(iii) *For products containing active ingredient(s) that provide an SPF value of 30 or above.* ''high sun protection product.''

(2) *For products containing any ingredient identified in § 352.10, the following labeling statement may be used under the heading ''Other information'' or anywhere outside of the ''Drug Facts'' box or enclosure.* ''Sun alert: Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun.'' Any variation of this statement will cause the product to be misbranded under section 502 of the act.

(f) *Products labeled for use only on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes) and that meet the criteria established in § 201.66(d)(10) of this chapter.* The title, headings, subheadings, and information described in § 201.66(c) of this chapter shall be printed in accordance with the following specifications:

(1) The labeling shall meet the requirements of § 201.66(c) of this chapter except that the title, headings, and information described in § 201.66(c)(1), (c)(3), and (c)(7) may be omitted, and the headings, subheadings, and information described in § 201.66(c)(2), (c)(4), (c)(5), and (c)(6) may be presented as follows:

(i) The active ingredients (§ 201.66(c)(2) of this chapter) shall be listed in alphabetical order.

(ii) The heading and the indication required by § 201.66(c)(4) may be limited to: ''Use [in bold type] helps prevent sunburn.''

(iii) The ''external use only'' warning in § 201.66(c)(5)(i) of this chapter may be omitted.

(iv) The subheadings in § 201.66(c)(5)(iii) through (c)(5)(vii) of this chapter may be omitted, provided the information after the heading ''Warnings'' states: ''Keep out of eyes.'' and ''Stop use if skin rash occurs.''

(v) The warning in § 201.66(c)(5)(x) of this chapter may be limited to the following: ''Keep out of reach of children.''

(vi) For a lipstick, the warnings ''Keep out of eyes'' in § 352.52(f)(1)(iv) and ''Keep out of reach of children'' in § 352.52(f)(1)(v) and the directions in § 352.52(d) may be omitted.

(2) The labeling shall be printed in accordance with the requirements of § 201.66(d) of this chapter except that any requirements related to § 201.66(c)(1), (c)(3), and (c)(7), and the horizontal barlines and hairlines described in § 201.66(d)(8), may be omitted.

§ 352.60 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading ''Uses,'' the indication(s) for each ingredient in the combination as established in the indications sections of the applicable

OTC drug monographs, unless otherwise stated in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established in the applicable OTC drug monographs or listed in this paragraph (b), may also be used, as provided by § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) In addition, the labeling of the product may contain any of the ''other allowable statements'' that are identified in the applicable monographs.

(2) For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

(c) *Warnings*. The labeling of the product states, under the heading ''Warnings,'' the warning(s) for each ingredient in the combination, as established in the warnings section of the applicable OTC drug monographs. For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

(d) *Directions*. The labeling of the product states, under the heading ''Directions,'' directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and may not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient. For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

Subpart D—Testing Procedures

§ 352.70 Standard sunscreen.

(a) *Laboratory validation.* A standard sunscreen shall be used concomitantly in the testing procedures for determining the SPF value of a sunscreen drug product to ensure the uniform evaluation of sunscreen drug products. The standard sunscreen shall be an 8-percent homosalate preparation with a mean SPF value of 4.47 (standard deviation = 1.279). In order for the SPF determination of a test product to be considered valid, the SPF of the standard sunscreen must fall within the standard deviation range of the expected SPF (i.e., 4.47 ± 1.279) and the 95-percent confidence interval for the mean SPF must contain the value 4.

(b) *Preparation of the standard homosalate sunscreen.*

(1) The standard homosalate sunscreen is prepared from two different preparations (preparation A and preparation B) with the following compositions:

COMPOSITION OF PREPARATION A AND PREPARATION B OF THE STANDARD SUNSCREEN

Ingredients	Percent by weight
Preparation A	
Lanolin	5.00
Homosalate	8.00
White petrolatum	2.50
Stearic acid	4.00
Propylparaben	0.05
Preparation B	
Methylparaben	0.10
Edetate disodium	0.05
Propylene glycol	5.00
Triethanolamine	1.00
Purified water U.S.P	74.30

(2) Preparation A and preparation B are heated separately to 77 to 82 °C, with constant stirring, until the contents of each part are solubilized. Add preparation A slowly to preparation B while stirring. Continue stirring until the emulsion formed is cooled to room temperature (15 to 30 °C). Add sufficient purified water to obtain 100 grams of standard sunscreen preparation.

(c) *Assay of the standard homosalate sunscreen.* Assay the standard homosalate sunscreen preparation by the following method to ensure proper concentration:

(1) *Preparation of the assay solvent.* The solvent consists of 1 percent glacial acetic acid (V/V) in denatured ethanol. The denatured ethanol should not contain a UV radiation absorbing denaturant.

(2) *Preparation of a 1-percent solution of the standard homosalate sunscreen preparation.* Accurately weigh 1 gram of the standard homosalate sunscreen preparation into a 100-milliliter volumetric flask. Add 50 milliliters of the assay solvent. Heat on a steam bath and mix well. Cool the solution to room temperature (15 to 30 °C). Then dilute the solution to volume with the assay solvent and mix well to make a 1-percent solution.

(3) *Preparation of the test solution (1:50 dilution of the 1-percent solution).* Filter a portion of the 1-percent solution through number 1 filter paper. Discard the first 10 to 15 milliliters of the filtrate. Collect the next 20 milliliters of the filtrate (second collection). Add 1 milliliter of the second collection of the filtrate to a 50-milliliter volumetric flask. Dilute this solution to volume with assay solvent and mix well. This is the test solution (1:50 dilution of the 1-percent solution).

(4) *Spectrophotometric determination.* The absorbance of the test solution is measured in a suitable double beam spectrophotometer with the assay solvent and reference beam at a wavelength near 306 nanometers.

(5) *Calculation of the concentration of homosalate.* The concentration of homosalate is determined by the following formula which takes into consideration the absorbance of the sample of the test solution, the dilution of the 1-percent solution (1:50), the weight of the sample of the standard homosalate sunscreen preparation (1 gram), and the standard absorbance value (172) of homosalate as determined by averaging the absorbance of a large number of batches of raw homosalate:

Concentration of homosalate = absorbance x 50 x 100 x 172 = percent concentration by weight.

§ 352.71 Light source (solar simulator).

A solar simulator used for determining the SPF of a sunscreen drug product should be filtered so that it provides a continuous emission spectrum from 290 to 400 nanometers similar to sunlight

at sea level from the sun at a zenith angle of 10 °; it has less than 1 percent of its total energy output contributed by nonsolar wavelengths shorter than 290 nanometers; and it has not more than 5 percent of its total energy output contributed by wavelengths longer than 400 nanometers. In addition, a solar simulator should have no significant time-related fluctuations in radiation emissions after an appropriate warmup time, and it should have good beam uniformity (within 10 percent) in the exposure plane. To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, it must be measured periodically with an accurately-calibrated spectroradiometer system or equivalent instrument.

§ 352.72 General testing procedures.

(a) *Selection of test subjects (male and female).*

(1) Only fair-skin subjects with skin types I, II, and III using the following guidelines shall be selected:

Selection of Fair-skin Subjects

Skin Type and Sunburn and Tanning History (Based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure.)

I—Always burns easily; never tans (sensitive).

II—Always burns easily; tans minimally (sensitive).

III—Burns moderately; tans gradually (light brown) (normal).

IV—Burns minimally; always tans well (moderate brown) (normal).

V—Rarely burns; tans profusely (dark brown) (insensitive).

VI—Never burns; deeply pigmented (insensitive).

(2) A medical history shall be obtained from all subjects with emphasis on the effects of sunlight on their skin. Ascertain the general health of the individual, the individual's skin type (I, II, or III), whether the individual is taking medication (topical or systemic) that is known to produce abnormal sunlight responses, and whether the individual is subject to any abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(b) *Test site inspection.* The physical examination shall determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. The presence of nevi, blemishes, or moles will be acceptable if in the physician's judgment they will not interfere with the study results. Excess hair on the back is acceptable if the hair is clipped or shaved.

(c) *Informed consent.* Legally effective written informed consent must be obtained from all individuals.

(d) *Test site delineation*—(1) *Test site area.* A test site area serves as an area for determining the subject's MED after application of either the sunscreen standard or the test sunscreen product, or for determining the subject's MED when the skin is unprotected (control site). The area to be tested shall be the back between the beltline and the shoulder blade (scapulae) and lateral to the midline. Each test site area for applying a product or the standard sunscreen shall be a minimum of 50-square centimeters, e.g., 5 x 10 centimeters. The test site areas are outlined with ink. If the person is to be tested in an upright position, the lines shall be drawn on the skin with the subject upright. If the subject is to be tested while prone, the markings shall be made with the subject prone.

(2) *Test subsite area.* Each test site area shall be divided into at least three test subsite areas that are at least 1 square centimeter. Usually four or five subsites are employed. Each test subsite within a test site area is subjected to a specified dosage of UV radiation, in a series of UV radiation exposures, in which the test site area is exposed for the determination of the MED.

(e) *Application of test materials.* To ensure standardized reporting and to define a product's SPF value, the application of the product shall be expressed on a weight basis per unit area which establishes a standard film. Both the test sunscreen product and the standard sunscreen application shall be 2 milligrams per square centimeter. For oils and most lotions, the viscosity is such that the material can be applied with a volumetric syringe. For creams, heavy gels, and butters, the product shall be warmed slightly so that it can be applied volumetrically. On heating, care shall

be taken not to alter the product's physical characteristics, especially separation of the formulations. Pastes and ointments shall be weighed, then applied by spreading on the test site area. A product shall be spread by using a finger cot. If two or more sunscreen drug products are being evaluated at the same time, the test products and the standard sunscreen, as specified in § 352.70, should be applied in a blinded, randomized manner. If only one sunscreen drug product is being tested, the testing subsites should be exposed to the varying doses of UV radiation in a randomized manner.

(f) *Waiting period.* Before exposing the test site areas after applying a product, a waiting period of at least 15 minutes is required.

(g) *Number of subjects.* A test panel shall consist of not more than 25 subjects with the number fixed in advance by the investigator. From this panel, at least 20 subjects must produce valid data for analysis.

(h) *Response criteria.* In order that the person who evaluates the MED responses does not know which sunscreen formulation was applied to which site or what doses of UV radiation were administered, he/she must not be the same person who applied the sunscreen drug product to the test site or administered the doses of UV radiation. After UV radiation exposure from the solar simulator is completed, all immediate responses shall be recorded. These include several types of typical responses such as the following: An immediate darkening or tanning, typically greyish or purplish in color, fading in 30 to 60 minutes, and attributed to photo-oxidation of existing melanin granules; immediate reddening, fading rapidly, and viewed as a normal response of capillaries and venules to heat, visible and infrared radiation; and an immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating to the skin's surface. After the immediate responses are noted, each subject shall shield the exposed area from further UV radiation for the remainder of the test day. The MED is determined 22 to 24 hours after exposure. The erythema responses of the test subject should be evaluated under the following conditions: The source of illumination should be either a tungsten light bulb or a warm white fluorescent light bulb that provides a level of

illumination at the test site within the range of 450 to 550 lux, and the test subject should be in the same position used when the test site was irradiated. Testing depends upon determining the smallest dose of energy that produces redness reaching the borders of the exposure site at 22 to 24 hours postexposure for each series of exposures. To determine the MED, somewhat more intense erythemas must also be produced. The goal is to have some exposures that produce absolutely no effect, and of those exposures that produce an effect, the maximal exposure should be no more than twice the total energy of the minimal exposure.

(i) *Rejection of test data.* Test data shall be rejected if the exposure series fails to elicit an MED response on either the treated or unprotected skin sites, or if the responses on the treated sites are randomly absent (which indicates the product was not spread evenly), or if the subject was noncompliant (e.g., subject withdraws from the test due to illness or work conflicts, subject does not shield the exposed testing sites from further UV radiation until the MED is read, etc.).

§ 352.73 Determination of SPF value.

(a)(1) The following erythema action spectrum shall be used to calculate the erythema effective exposure of a solar simulator:

$V_i\ (\lambda) = 1.0\ (250 < \lambda < 298\ \text{nm})$

$V_i\ (\lambda) = 1.0^{0.094\ (298\ -\ \lambda)}\ (298 < \lambda < 328\ \text{nanometers})$

$V_i\ (\lambda) = 1.0^{0.015\ (139\ -\ \lambda)}\ (328 < \lambda < 400\ \text{nanometers})$

(2) The data contained in this action spectrum are to be used as spectral weighting factors to calculate the erythema effective exposure of a solar simulator as follows:

$$E = \sum_{250}^{400} V_i(\lambda) * I(\lambda) * t_{exp}$$

where: E = Erythema Effective Exposure (dose: Joules per square meter)

V_i = Weighting Factor (Erythema Action Spectrum)

I = Spectral Irradiance (Watts per square meter per nanometer)

t_{exp} = exposure time (seconds)

where: E = Erythema Effective Exposure (dose: Joules per square meter)

V_i = Weighting Factor (Erythema Action Spectrum)

I = Spectral Irradiance (Watts per square meter per nanometer)

t_{exp} = exposure time (seconds)

(b) *Determination of MED of the unprotected skin.* A series of UV radiation exposures expressed as Joules per square meter (adjusted to the erythema action spectrum calculated according to § 352.73(a)) is administered to the subsite areas on each subject with an accurately calibrated solar simulator. A series of five exposures shall be administered to the untreated, unprotected skin to determine the subject's inherent MED. The doses selected shall be a geometric series represented by (1.25^n), wherein each exposure time interval is 25 percent greater than the previous time to maintain the same relative uncertainty (expressed as a constant percentage), independent of the subject's sensitivity to UV radiation, regardless of whether the subject has a high or low MED. Usually, the MED of a person's unprotected skin is determined the day prior to testing a product. This MED(US) shall be used in the determination of the series of UV radiation exposures to be administered to the protected site in subsequent testing. The MED(US) should be determined again on the same day as the standard and test sunscreens and this MED(US) should be used in calculating the SPF.

(c) *Determination of individual SPF values.* A series of UV radiation exposures expressed as Joules per square meter (adjusted to the erythema action spectrum calculated according to § 352.73(a)) is administered to the subsite areas on each subject with an accurately-calibrated solar simulator. A series of seven exposures shall be administered to the protected test sites to determine the MED of the protected skin (MED(PS)). The doses selected shall consist of a geometric series of five exposures, where the middle exposure is placed to yield the expected SPF plus two other exposures placed symmetrically around the middle exposure. The exact series of exposures to be given to the protected skin shall be determined by the previously established MED(US) and the expected SPF of the test sunscreen. For products with an expected SPF less than 8, the exposures

shall be the MED(US) times 0.64X, 0.80X, 0.90X, 1.00X, 1.10X, 1.25X, and 1.56X, where X equals the expected SPF of the test product. For products with an expected SPF between 8 and 15, the exposures shall be the MED(US) times 0.69X, 0.83X, 0.91X, 1.00X, 1.09X, 1.20X, and 1.44X, where X equals the expected SPF of the test product. For products with an expected SPF greater that 15, the exposures shall be the MED(US) times 0.76X, 0.87X, 0.93X, 1.00X, 1.07X, 1.15X, and 1.32X, where X equals the expected SPF of the test product. The MED is the quantity of erythema-effective energy required to produce the first perceptible, unambiguous redness reaction with clearly defined borders at 22 to 24 hours postexposure. The SPF value of the test sunscreen is then calculated from the dose of UV radiation required to produce the MED of the protected skin and from the dose of UV radiation required to produce the MED of the unprotected skin (control site) as follows:

SPF value = the ratio of erythema effective exposure (Joules per square meter) (MED(PS)) to the erythema effective exposure (Joules per square meter) (MED(US)).

(d) *Determination of the test product's SPF value and PCD.* Use data from at least 20 test subjects with n representing the number of subjects used. First, for each subject, compute the SPF value as stated in § 352.73(b) and (c). Second, compute the mean SPF value, $\bar{x}$, and the standard deviation, s, for these subjects. Third, obtain the upper 5-percent point from the t distribution table with n-1 degrees of freedom. Denote this value by t. Fourth, compute $ts/\sqrt{n}$. Denote this quantity by A (i.e., $A = ts/\sqrt{n}$). Fifth, calculate the SPF value to be used in labeling as follows: the label SPF equals the largest whole number less than $\bar{x} - A$. Sixth and last, the drug product is classified into a PCD as follows: if $30 + A < \bar{x}$, the PCD is High; if $12 + A < \bar{x} < 30 + A$, the PCD is Moderate; if $2 + A < \bar{x} < 12 + A$, the PCD is Minimal; if $\bar{x} < 2 + A$, the product shall not be labeled as a sunscreen drug product and shall not display an SPF value.

§ 352.76 Determination if a product is water resistant or very water resistant.

The general testing procedures in § 352.72 shall be used as part of the following tests, except where modified in this section. An indoor fresh water pool, whirlpool, and/or jacuzzi maintained

at 23 to 32 °C shall be used in these testing procedures. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity shall be recorded.

(a) *Procedure for testing the water resistance of a sunscreen product.* For sunscreen products making the claim of ''water resistant,'' the label SPF shall be the label SPF value determined after 40 minutes of water immersion using the following procedure for the water resistance test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period (do not towel test sites).

(4) 20 minutes moderate activity in water.

(5) Conclude water test (air dry test sites without toweling).

(6) Begin solar simulator exposure to test site areas as described in § 352.73.

(b) *Procedure for testing a very water resistant sunscreen product.* For sunscreen products making the claim of ''very water resistant,'' the label SPF shall be the label SPF value determined after 80 minutes of water immersion using the following procedure for the very water resistant test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period (do not towel test sites).

(4) 20 minutes moderate activity in water.

(5) 20-minute rest period (do not towel test sites).

(6) 20 minutes moderate activity in water.

(7) 20-minute rest period (do not towel test sites).

(8) 20 minutes moderate activity in water.

(9) Conclude water test (air dry test sites without toweling).

(10) Begin solar simulator exposure to test site areas as described in § 352.73.

§ 352.77 Test modifications.

The formulation or mode of administration of certain products may require modification of the testing procedures in this subpart. In addition, alternative methods (including automated or in vitro procedures) employing the same basic procedures as those described in this subpart may be used. Any proposed modification or alternative procedure shall be submitted as a petition in accord with § 10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative procedure provides results of equivalent accuracy. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

PART 700—GENERAL

4. The authority citation for 21 CFR part 700 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374.

5. Section 700.35 is added to subpart B to read as follows:

§ 700.35 Cosmetics containing sunscreen ingredients.

(a) A product that includes the term ''sunscreen'' in its labeling or in any other way represents or suggests that it is intended to prevent, cure, treat, or mitigate disease or to affect a structure or function of the body comes within the definition of a drug in section 201(g)(1) of the act. Sunscreen active ingredients affect the structure or function of the body by absorbing, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. These ingredients also help to prevent diseases such as sunburn and may reduce the chance of premature skin aging, skin cancer, and other harmful effects due to the sun when used in conjunction with limiting sun exposure and wearing protective clothing. When consumers see the term ''sunscreen'' or similar sun protection terminology in the labeling of a product, they expect the product to protect them in some way from the harmful effects of

the sun, irrespective of other labeling statements. Consequently, the use of the term ''sunscreen'' or similar sun protection terminology in a product's labeling generally causes the product to be subject to regulation as a drug. However, sunscreen ingredients may also be used in some products for nontherapeutic, nonphysiologic uses (e.g., as a color additive or to protect the color of the product). To avoid consumer misunderstanding, if a cosmetic product contains a sunscreen ingredient and uses the term ''sunscreen'' or similar sun protection terminology anywhere in its labeling, the term must be qualified by describing the cosmetic benefit provided by the sunscreen ingredient.

(b) The qualifying information required under paragraph (a) of this section shall appear prominently and conspicuously at least once in the labeling in conjunction with the term ''sunscreen'' or other similar sun protection terminology used in the labeling. For example: ''Contains a sunscreen—to protect product color.''

PART 740—COSMETIC PRODUCT WARNING STATEMENTS

6. The authority citation for 21 CFR part 740 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374.

7. Section 740.19 is added to subpart B to read as follows:

§ 740.19 Suntanning preparations.

The labeling of suntanning preparations that do not contain a sunscreen ingredient must display the following warning: ''Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn.'' For purposes of this section, the term ''suntanning preparations'' includes gels, creams, liquids, and other topical products that are intended to provide cosmetic effects on the skin while tanning through exposure to UV radiation (e.g., moisturizing or conditioning products), or to give the appearance of a tan by imparting color to the skin through the application of approved color additives (e.g.,

dihydroxyacetone) without the need for exposure to UV radiation. The term ''suntanning preparations'' does not include products intended to provide sun protection or otherwise intended to affect the structure or any function of the body.

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William K. Hubbard
Associate Commissioner for Policy Coordination

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